Interventions for orthodontically induced white spot lesions: a systematic review and meta-analysis

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Abstract: BACKGROUND Although orthodontic white spot lesions (WSLs) are one of the most often and most evident adverse effects of comprehensive fixed appliance treatment, the efficacy of interventions for WSLs has not yet been adequately assessed in an evidence-based manner. OBJECTIVE Aim of this systematic review was to assess the therapeutic and adverse effects of interventions to treat post-orthodontic WSLs from randomized trials in human patients. SEARCH METHODS An unrestricted electronic search of eight databases from inception to May 2016. SELECTION CRITERIA Randomized controlled trials assessing any interventions for post-orthodontic WSLs on human patients. DATA COLLECTION AND ANALYSIS After duplicate study selection, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of mean differences (MDs), standardized mean differences (SMDs), and odds ratios (ORs), including their 95% confidence intervals (CIs) were performed, followed by subgroup and sensitivity analyses. RESULTS A total of 20 unique studies and a total of 942 (42 per cent male and 58% per cent female) patients were included, with an average age of 16.2 years and a mean number of 8.2 WSLs (range 2.2 to 45.4) per patient. These were allocated to adjunct treatment with casein phosphopeptide-stabilized amorphous calcium phosphate creams, external tooth bleaching, low- or high-concentration fluoride films, gels, mouthrinses or varnishes, resin infiltration, miswak chewing sticks, bioactive glass toothpastse, or to no adjunct treatment (i.e. conventional oral hygiene). The monthly use of fluoride varnish was the best supplement to improve WSLs in terms of lesion area (1 trial; MD = -0.80 mm(2); 95% CI = -1.10, -0.50 mm(2); $P < 0.05$; high quality) and enamel fluorescence (3 trials; SMD = -0.92; 95% CI = -1.32, -0.52; $P < 0.05$; high quality), followed by the use of fluoride film. WSL treatment did not provide a considerable improvement in their clinical evaluation (3 trials; OR = 0.97; 95% CI = 0.60, 1.56; $P > 0.05$; moderate quality), with imprecision due to small sample size being the main limitation of existing evidence. CONCLUSIONS Based on the existing trials, interventions for post-orthodontic WSLs, mainly fluoride varnish, seem to be effective, but further research is needed to elucidate their clinical relevance. REGISTRATION PROSPERO (CRD42016037538).

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Title Page

Interventions for orthodontically-induced white spot lesions: a systematic review and meta-analysis

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Summary

Background: Although orthodontic white spot lesions (WSLs) are one of the most often and most evident adverse effects of comprehensive fixed appliance treatment, the efficacy of interventions for WSLs have not yet been adequately assessed in an evidence-based manner.

Objective: Aim of this systematic review was to assess the therapeutic and adverse effects of interventions to treat post-orthodontic WSLs from randomized trials on human patients.

Search methods: An unrestricted electronic search of eight databases from inception to May 2016.

Selection criteria: Randomized controlled trials assessing any interventions for post-orthodontic WSLs on human patients.

Data collection and analysis: After duplicate study selection, data extraction, and risk of bias assessment according to the Cochrane guidelines, random-effects meta-analyses of mean differences (MDs), standardized mean differences (SMDs), and odds ratios (ORs), including their 95% confidence intervals (CIs) were performed, followed by subgroup and sensitivity analyses.

Results: A total of 20 unique studies and a total of 942 (42% male/58% female) patients were included, with an average age of 16.2 years and a mean number of 8.2 WSLs (range 2.2 to 45.4) per patient. These were allocated to adjunct treatment with casein phosphopeptide-stabilized amorphous calcium phosphate creams, external tooth bleaching, low or high-concentration fluoride films, gels, mouthrinses or varnishs, resin infiltration, miswak chewing sticks, bioactive glass toothpastse or to no adjunct treatment (i.e. conventional oral hygiene). The monthly use of fluoride varnish was the best supplement to improve WSLs in terms of lesion area (1 trial; MD=-0.80; 95% CI=-1.10,-0.50; P<0.05; high quality) and enamel fluorescence (3 trials; SMD=-0.92; 95% CI=-1.32,-0.52; P<0.05; high quality), followed by the use of fluoride film. WSL treatment did not provide a considerable improvement in their clinical evaluation (3 trials; OR=0.97; 95% CI=0.60,1.56; P>0.05; moderate quality), with imprecision due to small sample size being the main limitation of existing evidence.

Conclusions: Based on existing trials, interventions for post-orthodontic WSLs, mainly fluoride varnish, seem to be effective, but further research is needed to elucidate their clinical relevance.

Registration: PROSPERO (CRD42016037538)

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Introduction

Rationale

Although fixed appliance treatment has become an integral part of modern orthodontics, it has also been associated with certain adverse effects. Among these, White Spot Lesions (WSLs) are, as they have a negative impact on the esthetic outcome of orthodontic treatment and might progress into carious lesions (1).

The reported prevalence of WSLs varies considerably, depending on the measurement method/ criteria, inclusion of pre-existing developmental enamel defects, and whether tooth surfaces, teeth or patients are used as reference unit. Wilmot and Brook (2) reported that every third (37%) treated patient had at least one new post-orthodontic WSL, while 24% of treated teeth developed at least one WSL (3), with the teeth most affected being the maxillary and mandibular first molars, maxillary lateral incisors, mandibular lateral incisors, and mandibular canines (4). Although treatment duration can influence the prevalence and severity of WSLs (5), WSLs can develop also within the first four weeks of fixed appliance treatment (6).

Several preventive measures have been suggested to avoid or reduce the development of WSLs during fixed appliance treatment, including fluoride-releasing glass ionomer cements for bonding and banding (5), daily use of a fluoride mouthrinse (7), and the use of lingual orthodontic appliances (8). A recent systematic review (7) found that although such preventive measures during orthodontic treatment might be promising in the short term, robust evidence on their effect during the complete span of orthodontic treatment is lacking.

After removal of fixed appliances a considerable improvement of WSLs is seen during the first 6-24 months (9). This observed clinical shrinkage or healing of WSLs after orthodontic treatment can be explained by three factors: (a) removal of an etiologic factor (cariogenic plaque adhered to fixed orthodontic elements) and the return of *S. mutans* and *Lactobacillus spp*. to their baseline levels (10) combined with (b) abrasion of the surface enamel during tooth brushing (9) and also (c) with remineralization through the use of a fluoride-containing dentifrice or-mouthrinse (5, 11–13). However, many WSLs persevere even a decade after appliance removal (9) and remain a cosmetic problem. Interventions for the treatment of WSLs after appliance removal move mainly in two axes. Firstly, remineralization of WSLs takes place naturally to a certain degree after appliance removal and the shift to a more enamel-friendly ecosystem (13). However, interventions such as topical fluoride, Casein Phosphopeptide Amorphous Calcium Phosphate (CPP-ACP), or self-assembling peptides have also been used as adjuncts to daily use of fluoride toothpaste to enhance remineralization and improve its efficacy. Secondly, other more invasive techniques like bleaching, the

hydrochloric acid-pumice microabrasion technique (14) or resin infiltration have been implemented in an attempt to improve the clinical appearance of WSLs.

Previous systematic reviews on the subject (15, 16) suffered from issues usually found in similar orthodontic publications (17-19) like limited literature search (15, 16) or no use of widely-accepted frameworks for the evaluation of the strength of evidence (15) or focused on a single category of interventions (15); none of them (15, 16) performed meta-analysis to quantify the treatment effects of the various interventions and the associated uncertainty around them.

Objectives

Aim of this present systematic review was to critically assess the evidence from randomized clinical trials on humans investigating interventions aimed to treat or alleviate WSLs of teeth that originated from a previous comprehensive fixed appliance therapy and to conduct meta-analysis, if possible.

Materials and Methods

Protocol and registration

The protocol for this review was made *a priori* based on the PRISMA-P statement (20), registered in PROSPERO (CRD42016037538), and all *post hoc* changes were appropriately noted. This systematic review was conducted and reported according to Cochrane Handbook (21) and PRISMA statement (22), respectively.

Eligibility criteria

According to the Participants-Intervention-Comparison-Outcome-Study design schema (PICOS), we included parallel or split-mouth randomized and quasi-randomized prospective controlled trials on human patients comparing any intervention for WSLs that were induced from a previous orthodontic treatment to a control/placebo group or to another intervention and assessing therapeutic effects (both effectiveness and efficacy) or adverse effects (Appendix 1). Excluded were non-clinical studies, retrospective studies, animal studies, and studies on intervention for the prevention or treatment of WSLs during orthodontic treatment.

Information sources and literature search

A total of eight electronic databases were searched systematically by two authors (DM, MHZ) without any limitations from inception up to May 9th, 2016 (Appendix 2). Two additional sources (Google Scholar and ISRCTN registry)

were manually searched for additional trials or protocols by the same authors. Authors of included trials were contacted for additional missed or ongoing trials. No limitations concerning language, publication year or status were applied. The reference lists and citation lists of the included trials and relevant reviews were manually searched as well.

Study selection

Titles identified from the search were screened by one author (DM) with a subsequent duplicate independent checking of their abstracts/full-texts against the eligibility criteria by a second author (MHZ), while conflicts were resolved by a third author (SNP).

Data collection

Characteristics of included trials and numerical data were extracted in duplicate by two authors (DM, MHZ) using pre-determined and piloted extraction forms. Piloting of the forms was performed during the protocol stage until over 90% agreement was reached. Missing or unclear information was requested by the trials' authors.

Risk of bias in individual trials

The risk of bias of the included trials was assessed using Cochrane's risk of bias tool (21) after initial calibration. A main risk of bias assessment was included in the systematic review pertaining to each trial's primary outcome.

Data synthesis

As the outcome of WSL treatment is bound to be affected by the initial lesion characteristics, used substance, company, and procedure used, as well as patient characteristics, a random-effects model according to DerSimonian and Laird (23) was deemed appropriate to incorporate this variability (24).

The Mean Difference (MD) and the Odds Ratio (OR) with their corresponding 95% Confidence Interval (CI) were chosen as effect measures for continuous and binary outcomes, respectively. For split-mouth trials, where clustering was not taken into account during the analysis, we additionally tried to contact the trial's authors to request raw data or clustering-adjusted estimates.

Between-trial heterogeneity was quantified with the I^2 statistic, defined as the proportion of total variability in the results explained by heterogeneity, and not chance (25). The 95% uncertainty intervals (95% UI) (similar to CIs) around the I^2 were calculated (26) using the non-central χ^2 approximation of Q (27). 95% predictive intervals were

calculated for meta-analyses of three trials or more, which incorporate existing heterogeneity and provide a range of possible effects for a future clinical setting (19). All analyses were run in Stata SE 10.0 (StataCorp, College Station, TX) by one author (SNP). A two-tailed P-value < 0.05 was considered significant for hypothesis-testing, except for P < 0.10 used for the test of heterogeneity (28).

Risk of bias across studies

The overall quality of evidence for each of the main outcomes was rated as very low, low, moderate or high using the GRADE approach (18). For this assessment, the risk of bias of each included trial was re-assessed separately at outcome level.

The minimal clinical important, large, and very large effects were conventionally defined (29) as half, one, and two standard deviations, respectively. The standard deviation for an outcome was averaged from control groups of the existing trials. Conventional cut-offs of 1.5, 2.5, and 4.3 were adopted for the OR. The produced forest plots were augmented with contours denoting the magnitude of the observed effects (30). Finally, the optimal information size (i.e. required meta-analysis sample size) was calculated for each outcome independently for $\alpha = 5\%$ and $\beta = 20\%$.

Additional analyses

Possible sources of heterogeneity were planned to be sought through pre-specified mixed-effects subgroup analyses and random-effects meta-regression with the Knapp and Hartung (31) adjustment in meta-analyses of at least five trials. Indications of reporting biases (including small-study effects) were planned to be assessed with Egger's linear regression test (32) and contour-enhanced funnel plots, should ten or more trials be pooled.

Sensitivity analyses

Robustness of the results was planned *a priori* to be checked with sensitivity analyses based on (i) inclusion/exclusion of trials with low risk of bias, (ii) improvement of the GRADE classification, and (iii) inclusion/exclusion of cluster randomized trials. We additionally performed two *post hoc* sensitivity analyses: one to investigate the robustness of different WSL evaluation methods and one to assess the effect of included number of WSLs/ patient on the results.

Results

Study selection

A total of 594 and 37 papers were identified through electronic (Appendix 2) and manual searches, respectively (Fig. 1). After removal of duplicates and initial screening, 55 papers were assessed using the eligibility criteria, and 22 papers were included in this systematic review (Fig. 1; Appendix 3). In one instance, duplicate publications pertaining to the same trial were grouped together; thus, a total of 20 trials from 22 publications were finally included in the systematic review.

Study characteristics

The characteristics of the trials included can be seen in Table 1. Of the 20 trials included, 17 (85%) were parallel randomized and 3 (15%) were cluster randomized trials, conducted in 12 different countries. They included a total of 942 patients (mean 47.1; range 11 to 211) with at least 338 male (42.4%) and 460 female (57.6%) patients (gender was not specified in five trials), and with an average age of 16.1 years. Where the information was available, the WSLs that were acquired during the orthodontic fixed appliance phase were treated either directly following debonding or after an intermediate period of up to 14 years. According to their eligibility criteria and protocol, the included trials reported a mean of 8.2 WSLs per patient (range 2.2 to 45.4). A wide variety of interventions were used to treat the WSLs including CPP-ACP creams (with or without fluoride), external tooth bleaching, low or high-concentration fluoride materials (in form of film, gel, mouthrinse, toothpaste or varnish), resin infiltration, miswak chewing sticks or bioactive glass toothpaste. After application, the patients were followed for periods ranging from a couple weeks to 6.5 months and investigated outcomes included among others clinical assessments, intraoral photographs, QLF or laser fluorescence methods, estimation of tooth color according to CIE, and patient questionnaires (Table 1).

Risk of bias within studies

The risk of bias assessment for the 20 trials included is shown in Fig. 2. High risk of bias was found in 11 trials (55%) for at least one bias domain. The most problematic domains were the blinding of outcome assessors (problematic in 30% of the trials), followed by selective reporting (found in 25% of the trials), and other risk of bias (found in 15% of the trials). The detailed risk of bias assessment for each trial and each domain can be seen in Appendix 4.

Results of individual studies and data synthesis

From the 20 unique trials (22 papers) that were included in the systematic review, three reported incomplete data and therefore could not be included in a meta-analysis (Figure 1) and although the authors were contacted, we took no

response. The quantitative results of individual studies and the performed meta-analyses are presented in Table 2. In all instances the MD and the OR were used for continuous and binary outcomes, respectively, with the exception of the tooth fluorescence outcome. Included studies that assessed tooth fluorescence used either QLF or laser fluorescence methods and therefore the Standardized Mean Difference (SMD) was used to pool these two measures together, while a *post hoc* sensitivity analysis was conducted to check the robustness of this choice. In cases of original trials that report results at baseline and at a following timepoint, we converted these into treatment-induced increments at the longest follow-up (after-treatment minus before-treatment). The needed pre-post correlation was calculated from the trial of Wilmot (35), which was the only one that provided raw data in the published paper. In almost all instances the included trials compared various interventions with a control/placebo group. The only exception is the trial of Andersson *et al.* (36) that compared head-on-head two interventions and its results are provided separately in Table 2. For all other cases, multiple trial arms were pooled within a trial before being compared to the control group to avoid double-counting of the control patients (21).

As far as efficacy is concernced, statistically significant overall improvements were found between intervention and control groups for various optical outcomes of tooth color according to CIE L*a*b color space, which is a color-opponent space with the dimension *L* for lightness and *a* and *b* as the color-opponent dimensions. Additinally, statistically significant improvements after treatment were found for the clinical evaluation of WSLs either with the International Caries Detection and Assessment System II (ICDAS II) or other criteria. No adverse effects of interventions for post-orthodontic WSLs, apart from a single case of nausea after a patient swallowed a small portion of a fluoride varnish, reported from *He et al.* (37), which lasted for a day. However, the vast majority of comparisons were informed from a single trial.

Risk of bias across studies

Meta-analyses of at least three studies could be performed in just three instances: the outcomes of lesion area (Fig. 3), lesion fluorescence (Fig. 4), and clinical assessment of the lesion's improvement (Table 2); these were chosen as the review's main outcomes to be included in the Summary of Findings Table according to the GRADE approach (Table 3; Appendix 5). The overall quality of evidence was judged as low to moderate for the three outcomes, with the main reasons for downgrading being either inconsistency (due to heterogeneity) or imprecision (due to inadequate sample sizes).

Additional analyses

Subgroup analyses were conducted in order to determine the efficacy of every intervention separately (Appendix 6). As can be seen, considerable differences in the efficacy of the various treatments were found for the improvement in both lesion area and enamel fluorescence, which were also statistically significant according to the mixed-effect subgroup analysis. The bioactive glass toothpaste, the CPP-ACP cream with fluoride, and the fluoride varnish seemed to be the most effective in reducing the lesions' area (Appendix 7). On the other side, the fluoridated chewing sticks (miswaks), the fluoride varnish, and the fluoride film (an acidulated sodium fluoride film that is applied and molds on the teeth) seemed to be the most viable intervention to increase the enamel's fluorescence (Appendix 8).

The follow-up duration after administration of the treatment to the WSLs was not stignificantly associated with the intervention's effect on the lesion's area. However, significantly greater improvements of the enamel's fluorescence were seen with greater follow-ups (P=0.032; Appendix 9). This might not directly be associated with the administered treatment and could possibly be attributed to the prolonged use of fluoride toothpaste during this period.

The sensitivity analysis by excluding trials with high risk of bias indicated only minor difference in effect magnitude with consistent effect direction (Appendix 10). Overall, no statistically significantly differences were found, although this could also be attributed to the small sample size. Sensitivity analysis according to the mean number of WSLs per patient indicated that as the mean number of WSLs per patient increased, the improvement seemed to decrease significantly (Appendix 10-11). Although this should be interpreted with great caution, this might indicate that not all WSLs respond the same to the intervention and trials that assess few WSLs per patient tend to include only those that responded well. Additionally, the sensitivity analysis according to the measurement method for enamel fluorescence indicated that considerable differences existed between QLF and DIAGNOdent, where the latter yielded both greater and more imprecise values (Appendix 10 & 12).

Finally, a sensitivity analysis was performed in order to improve the overall quality of evidence according to GRADE. As the problem of imprecision could not be addressed, the issue of heterogeneity was addressed by breaking down the two heterogeneous outcomes of lesion area and enamel fluorescence in their subgroups according to intervention (Appendix 13). According to this analysis, the use of either fluoride varnish or fluoride film seemed to be the most attractive choice in terms of both outcomes. Even though this did not have the largest effect that was seen among trials, it was still the only choice that is supported by high quality of evidence and is still statistically significant. Therefore, it might be preferable to base clinical decisions for the outcomes of improvement of lesion area and enamel

fluorescence on the sensitivity analyses for each separate material rather than the main analyses, where all interventions all pooled, as the overall quality of evidence was poorer.

Discussion

Summary of evidence

This systematic review included 20 randomized and trials and a total of 942 patients. Although some evidence exists on the clinical performance of various interventions for post-orthodontic WSLs, the majority of this evidence originates from small trials with unclear reporting or considerable limitations in their planning, conduct, and reporting. Despite the advances in orthodontic materials and techniques during the last decades, treating resistant post-orthodontic WSLs still remain a challenge.

Overall, available interventions for WSLs provided a small, and possibly clinically irrelevant improvement of WSL in lesion area, enamel fluorescence, and clinical evaluation groups, compared to daily oral hygiene procedures. Both effects were not statistically significant (although close to), probably due to the small effects detected and the observed imprecision.

However, a wide variety of interventions was used in the included studies. Some researchers (39) have warned against the use of high-fluoride materials to treat WSLs in esthetically-demanding labial tooth surfaces, as the quick surface hypermineralization arrests further demineralization, but also remineralization of WSLs. Although this might be preferable in posterior lesions, instant arrest of an anterior lesion might also carry the risk of staining by organic debris and a subtler remineralization with more natural means (i.e. through saliva and low-fluoride materials) might be associated with more esthetically-pleasing and stable results (40, 41). Interestingly, the results of the meta-analyses according to the different interventions used (Figures 5-6), and especially the results of the sensitivity analyses (Appendix 13), indicated that a monthly fluoride supplementation in the form of a fluoride varnish of a fluoride film was the most effective protocol to enhance the "natural" remineralization that takes place due to toothbrushing with a fluoride-containing dentifrice. It has long been known that fluoride inhibits mineral loss during acid dissolution, enhances mineralization of dental enamel, and might also increase the enamel's resistance against demineralization (42–44). However, as He *et al.* (37) reported, interventions for WSLs mostly resulted in an improvement of the WSLs, while a complete healing of the WSL is seldom seen [in 2 of the 528 teeth included (37)]. The use of either a bioactive glass toothpaste or a fluoride-containing CPP-ACP cream was associated with above the average improvement in

lesion area, but as this originated from small trials with high risk of bias, caution is warranted by the interpretation of these findings and further confirmatory evidence is needed.

The evaluation method for WSLs is of paramount importance to the accurate detection or measurement of lesions, and therefore to clinical research comparing various modalities. Measurement of the lesion's area in the included trials was performed with either photographic evaluation or QLF and no significant difference between the two methods were found (Appendix 10; P=0.568), which indicates that the levels of validity, repeatability, and agreement between photographic measurements and QLF might be comparable (13, 35, 45, 46).

On the other hand, this doesn't seem to be the case for the assessment of the WSLs' fluorescence compared to healthy enamel. Two evaluation methods were used in the included trials: a laser fluorescence method based on the red end of the electromagnetic spectrum with light wavelength 655 nm (DIAGNODent, KaVo, Germany) or Quantitative Light-Induced Fluorescence (QLF), which uses a blue light lamp with peak intensity of 370 nm. The results of the sensitivity analyses indicated trials using DIAGNOdent reported significantly greater improvements in fluorescence compared to trials using QLF (Appendix 10; P=0.036). Additionally, the readings regarding the fluorescence improvement in the non-treated WSL with DIAGNOdent were more inconsistent than those with QLF (average standard deviation in the control groups of the included trials of 4.01 and 2.55 for DIAGNOdent and QLF, respectively). This seems to be in agreement with *in vitro* evidence, where the two methods were compared to the gold standard of histopathology and transverse microradiography that indicates that QLF might be a better method to evaluate mineral loss in carious lesions in enamel (46–48). Although the SMD was used in the main meta-analyses, which alleviates part of the variability in measurements and enables pooling of the two methods, it might be prudent to suggest that future trials prefer the use of QLF to WSLs, due to its better validity and repeatability (45, 46).

Most included trials had a small to modest follow-up of up to 6.5 months after treatment, which might have an impact on the observed results. Existing studies indicate that a "natural" improvement of WSLs takes place post-debond, which is more pronounced in the first 6 months (9, 13), but continues up to the 12^{th} month, and extends up to the second year post-debond (9). Indeed, meta-regression analysis indicated that the trials' follow-up period was significantly associated with the improvement of tooth fluorescence (P<0.05). Therefore, trials with extended follow-up periods might be preferable in order to investigate the complete healing of post-orthodontic WSLs.

Strengths and limitations

The strengths of this systematic review include it's *a priori* registration in PROSPERO (49), the extensive unrestricted literature search, the use of robust methodology pertaining to the qualitative and quantitative synthesis of data (50), the exclusion of biased study designs (51), transparent reporting of quantitative data for all outcomes from included studies, assessment of the quality of evidence with the GRADE approach (18), and the use of sensitivity analyses to check the robustness of the results to the risk of bias. However, some limitations are also present in this study. First and foremost, this systematic review included mostly small randomized trials, which can influence the results of the meta-analyses (52). Furthermore, despite our attempts (Appendix 14), no clarifications or additional outcome data could be obtained from many authors of included studies, many of which used possibly inappropriate analyses methods that disregarded the correlation of multiple WSLs within each patient. Such trials need to take clustering into account during the planning, conduct, and analysis stage (53), and failure to do so might impact their results (54). Finally, the limited number of included trials precluded robust assessments of heterogeneity, subgroup analyses, small-study effects, and reporting biases for most of the outcomes (Appendix 15).

Recommendations for clinical practice

Based on available overall evidence, current interventions for WSL, supplemental to daily tooth-brushing with a fluoride dentifrice, seem to have only a modest, and possibly clinically irrelevant, added value to the improvement of WSLs (low quality evidence). Among the available treatments, the monthly use of a 22,600 ppm F fluoride varnish or a 5% NaF film seem to be the best viable protocols to augment daily use of a fluoride dentifrice in terms of both reducing the WSL area and to increasing its esthetic appearance (fluorescence; high quality of evidence). The treatment effects of a bioactive glass toothpaste or a CPP-ACP cream with fluoride seem promising, but high uncertainty exists due to risk of bias and therefore need to be supported by high quality evidence before they can be recommended.

Recommendations for further research

The inclusion of additional parallel randomized trials or split-mouth randomized trials is needed. These should preferably use QLF methods in the assessment of enamel demineralization instead of the DIAGNOdent method and follow WSLs treated after debonding for 1-2 years. Additionally, future trials should take into account clustering during the statistical analyses in order to robustly assess the efficacy of various interventions for post-orthodontic WSLs, especially in the long term. Furthermore, well-conducted trials are needed to robustly assess the efficacy of several interventions with limited evidence including CPP-ACP creams with fluoride, bioactive glass dentifrices, bleaching,

microabrasion, and resin infiltration. The addition of more future trials will also consolidate the network of available interventions, which at the present time is somewhat scarcely connected (Appendix 16). This will enable the ranking of all available treatments according to their efficacy through network meta-analysis, which is considered to provide the highest level of treatment to inform treatment guidelines (55). Finally, given the complex character of the research question and the multiple treatment groups, outcomes, timepoints, and the effect clustering can have on a trial's conlusions, orthodontic researchers and journal editors are encouraged to support both the registration and the provision of widely publically available raw trial data to improve their credibility (56).

Supplementary material

Supplementary material is available at *European Journal of Orthodontics* online.

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Conflicts of interest

None.

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Figure legends

Figure 1. Flowdiagram for the identification and selection of studies in this systematic review.

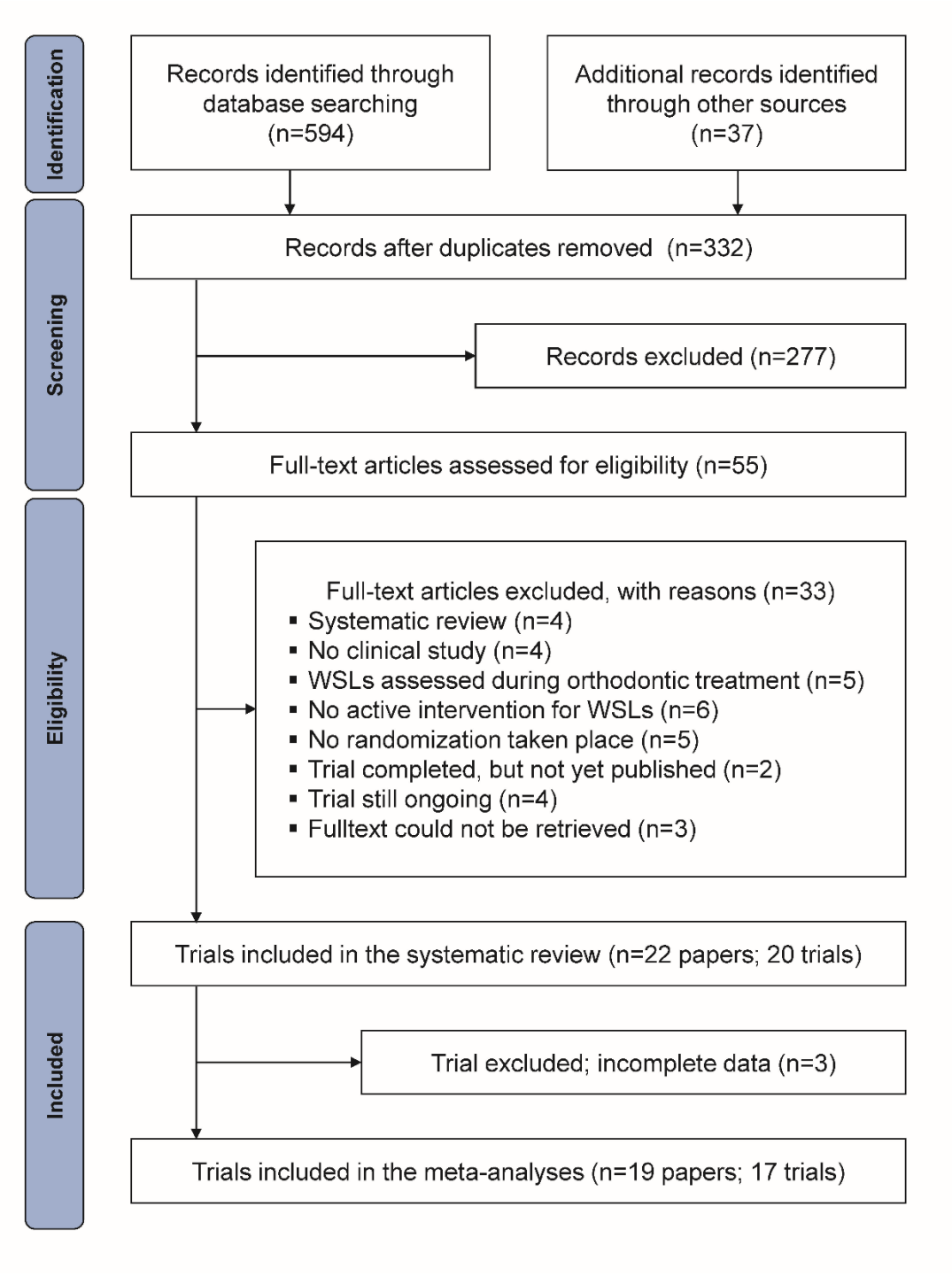

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Figure 2. Summary of the risk of bias of the trials included in this systematic review.

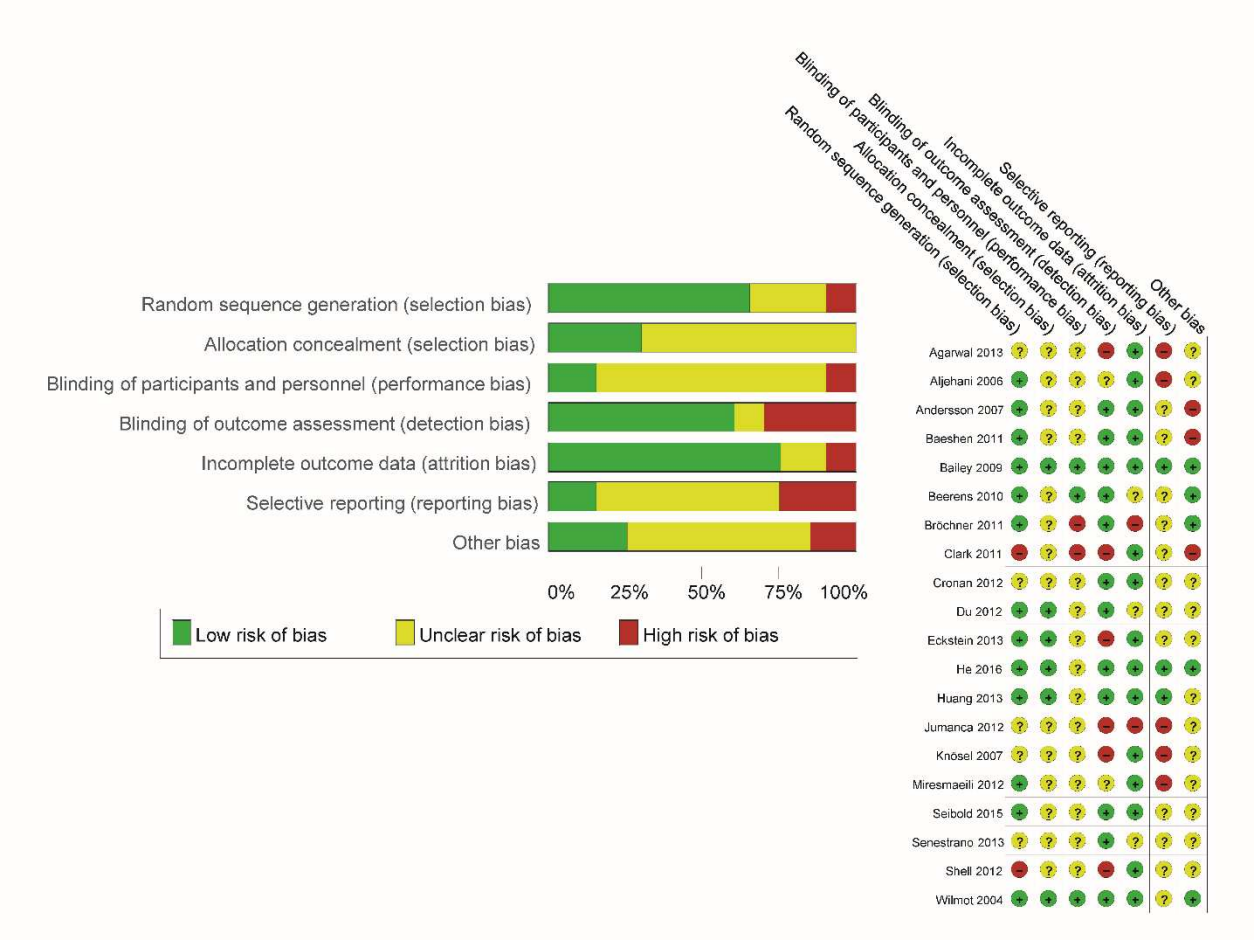

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Figure 3. Contour-enhanced forest plot of the treatment effects on white spot lesion area. Color contours indicate increasing effect magnitude from the middle to the ends of the forest plot: small effects (white); moderate effects (light grey); large effects (dark grey); and very large effects (darker grey). Mos, months of follow-up; MD; mean difference; CI, confidence interval; $_{comb}$, combined trial arms; and PrI, predictive interval. Studies on the left and the right side of the middle line favor the intervention and the control group, respectively.

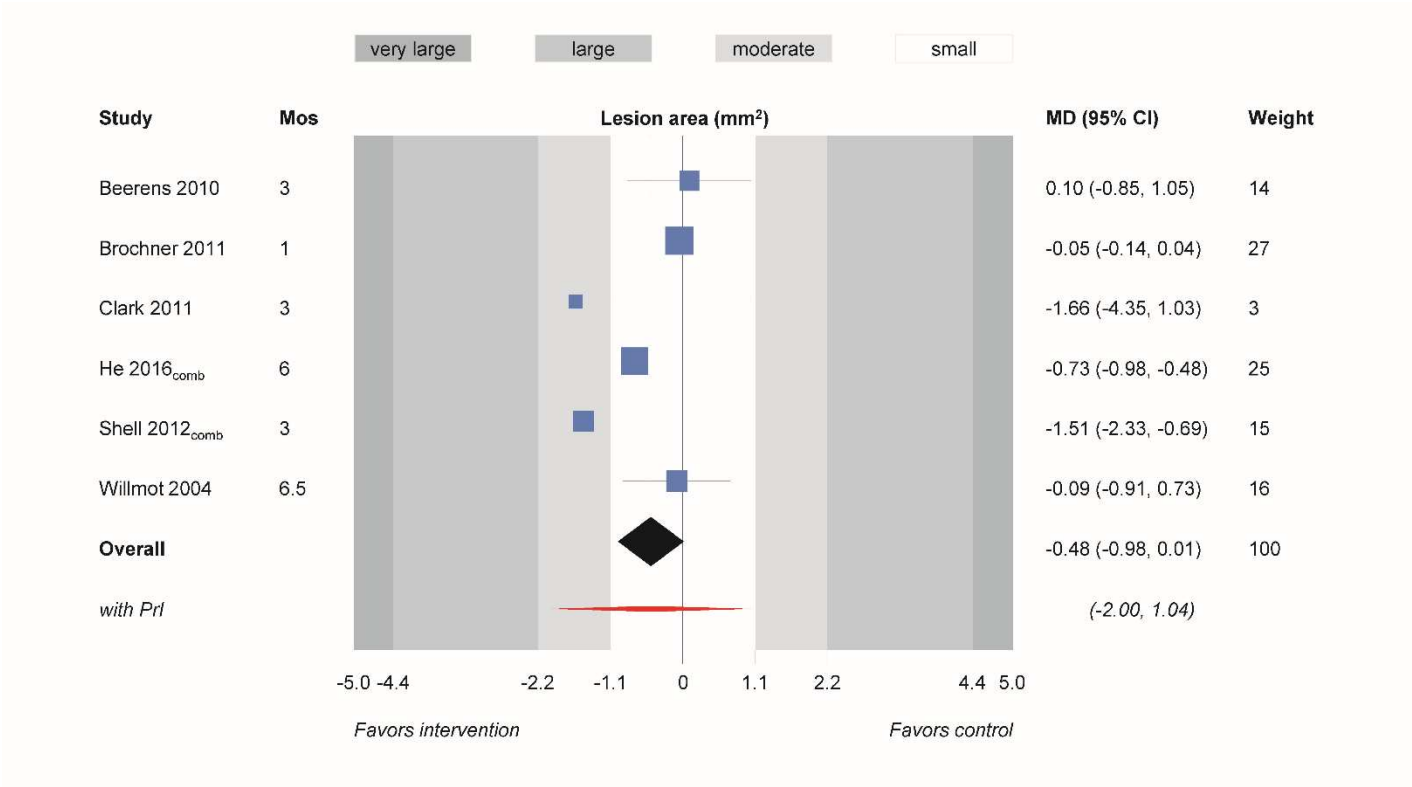

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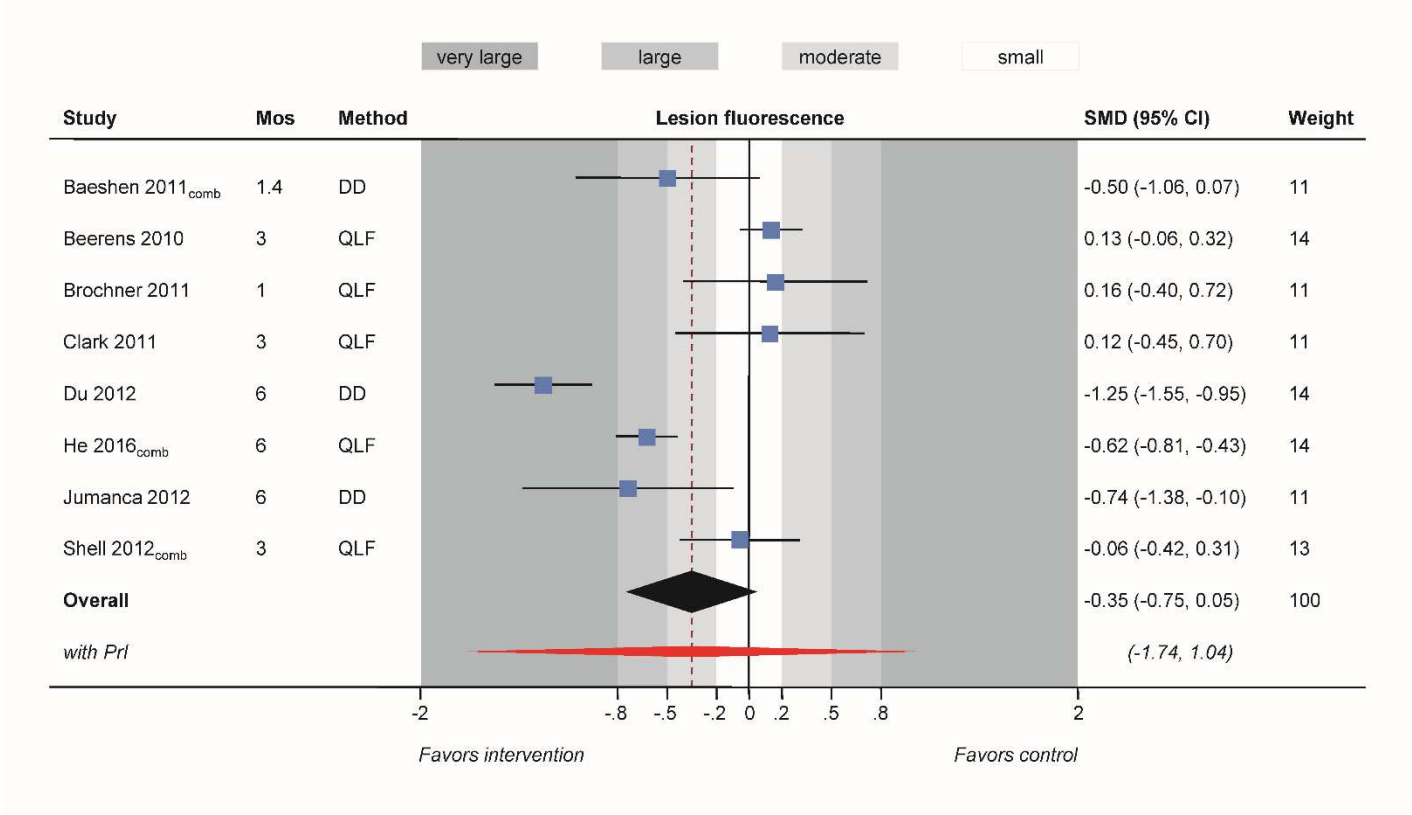
Figure 4. Contour-enhanced forest plot of the treatment effects on white spot lesion fluorescence. Color contours indicate increasing effect magnitude from the middle to the ends of the forest plot: small effects (white); moderate effects (light grey); large effects (dark grey); and very large effects (darker grey). Mos, months of follow-up; Method, method of outcome measurement; SMD; standardized mean difference; CI, confidence interval; $_{comb}$, combined trial arms; DD, DIAGNOdent; QLF, quantitative light-induced fluorescence; and PrI, predictive interval. Studies on the left and the right side of the middle line favor the intervention and the control group, respectively.



Tables

Table 1. Characteristics of the included trials.

AA	Trial	Design	Patients (M/F)	Mean age (yr)	Debond-Intervention period	WSLs/pat	Intervention	Other F sources	Follow-up	Outcome	Conflict of interest
1	Agarwal 2013	RCT_{SM}; university; India	31 (NR)	19.6	Directly	(≥4)	G1: F-TP (1450 ppm F) G2: Non- F-TP	-	8 wks	(Clin) ICDAS II	None
2	Aljehani 2006	RCT_{PAR}; hospital; Saudia Arabia	12 (NR)	(13-17)	NR (*recently*)	10.6	OHI plus: G1: PTC/ 3mos G2: Control	TP (provided; 1500 ppm F)	3/ 6/ 9/ 12 mos	-(Clin) Ekstrand *et al.* (33) criteria (mod.) -Fluoresence (DD)	Not declared
3	Andersson 2007	RCT_{PAR}; hospital; Sweden	26 (13/13)	14.6	Directly	5.1	G1: CPP-ACP cream (first 3mos) / F-TP (1000-1100 ppm F; next 3mos) G2: F-TP (1000-1100 ppm F) & F-MR (0.05% NaF); both 6mos	-	1/ 3/ 6/ 12 mos	-(Clin) Andersson *et al.* (34) criteria -Fluoresence (DD)	Not declared
4	Baeshen 2011	RCT_{PAR}; hospital; Saudi Arabia	37 (11/26)	17.2	Directly	7.9	G1: F-chewing sticks "Miswaks (0.5% NaF) G2: non-F-Miswaks	TP (instructed; 1450 ppm F)	2/ 4/ 6 wks	-(Clin) ICDAS II -Fluoresence (DD)	None
5	Bailey 2009	RCT_{PAR}; private practice; Australia	45 (22/23)	15.5	Directly	9.1	G1: CPP-ACP cream G2: Placebo cream	-TP (instructed; 1000 ppm F) -MR (900 ppm F)/ 4wks	4/ 8/ 12 wks	(Clin) ICDAS II	Not declared; trial partly funded by a company.
6	Beerens 2010[$]	RCT_{PAR}; university; Netherlands	54 (23/31)	15.5	Directly	7.9	G1: CPP-ACP cream (900 ppm F) G2: Control (non- F-TP)	TP (instructed; NR ppm F)	6/ 12 wks	QLF imaging	Not declared; material donation.
7	Bröchner 2011	RCT_{PAR}; university; Denmark	60 (27/33)	15.2	NR	6.5	G1: CPP-ACP cream G2: Control	TP (provided; 1100 ppm F)	4/ 12 wks	-(Clin) Gorelick *et al.* (1) criteria -QLF imaging	None; partial funding and material donation from a company.
8	Clark 2011	RCT_{PAR}; university; USA	12 (5/7)	(12-20)	1-2 wks	3.9	G1: CPP-ACP cream (900 ppm F) G2: Control	TP (provided; NR ppm F)	3/ 6/ 9/ 12 wks	-(Clin) Photograph -QLF imaging	Not declared
9	Cronan 2012	RCT_{SM}; university; USA	11 (7/4)	16.5	6 mos – 14 yrs	45.4	G1: Resin infiltrant G2: Control	-	4/ 6 wks	-EDI (mod.)	Not declared
10	Du 2012	RCT_{PAR}; university; China	96 (31/65)	16.6	Directly	2.2	G1: F varnish (22,600 ppm F)/ mo G2: Saline solution/ mo	TP (instructed; F concentration NR)	3/ 6 mos	Fluoresence (DD)	None
11	Eckstein 2013; Knösel 2013; Eckstein 2015	RCT_{SM}; university; Germany	21 (10/11)	15.5	1-12 mos	11.0	G1: Resin infiltrant G2: Control	TP (provided; 1400 ppm F)	1 d/ 1/ 4 wks/ 3/ 6 mos	CIE L*a*b values	Not declared; grant and intervention material donation from a company.

12	He 2016	RCT_{PAR}; university; China	211 (94/117)	16.9	NR (*recently*)	2.5	G1: F varnish (22,600 ppm F)/ mo G2: F film (5% NaF)/ mo G3: Placebo toothpaste/ mo	TP (provided; F concentration NR)	3/ 6 mos	QLF imaging	None
13	Huang 2013	RCT_{PAR}; private practice; USA	115 (56/59)	14.4	≤2 mos	3.2	G1: CPP-ACP cream (900 ppm F) G2: F varnish (22,600 ppm F)/mo G3: Control	TP (provided; 1100 ppm F)	8 wks	-(Clin) Photograph -Patient satisfaction (VAS)	None
14	Jumanca 2012	RCT_{PAR}; university; Romania	62 (NR)	(13-22)	Directly	(≥2)	G1: Resin infiltrant G2: F varnish (22,600 ppm F)/mo G3: Control	-	3/ 6 mos	Fluoresence (DD)	Not declared
15	Knösel 2007	RCT_{PAR}; university; Germany	19 (NR)	NR	<3 mos	3.7	G1: External bleaching (1 x in-office/ 1 x at-home) G2: Control	F gel (instructed; 12,500 ppm F)	2/ 4 wks	-CIE L*a*b values -Patient satisfaction (VAS)	Not declared
16	Miresmaeili 2012	RCT_{PAR}; university; Iran	20 (4/16)	NR	NR	3.1	G1: F varnish (22,600 ppm F)/mo G2: Control	-	4 mos	(Clin) Photograph	Not declared
17	Seibold 2015	RCT_{PAR}; university; Germany	39 (17/22)	15.3	Directly	(≥1)	G1: F gel (12,500 ppm F)/wk G2: Placebo gel/wk	TP (provided; 1400 ppm F)	1/ 2/ 6/ 12/ 24 wks	-(Clin) Photograph -CIE L*a*b values -ICDAS II - Gorelick *et al.* (1) criteria -DMFT index	Not declared; sponsored from company.
18	Senestraro 2013	RCT_{PAR}; university; USA	20 (NR)	16.6	12.3 mos	3.3	G1: Resin infiltrant G2: Control	TP (provided; F concentration NR)	8 wks	(Clin) Photograph & VAS	None; intervention material donated from a company.
19	Shell 2012	RCT_{PAR}; university; USA	30 (12/18)	16.1	NR (*recently*)	5.9	G1: CPP-ACP cream G2: CPP-ACP cream (900 ppm F) G3: CPP-ACP cream (900 ppm F) (in-office & at-home) G4: BA TP (5000 ppm F) G5: Control	TP (provided; 1100 ppm F)	3 mos	-(Clin) Photograph -QLF imaging	Not declared
20	Willmot 2004	RCT_{PAR}; university; UK	21 (6/15)	15.8	Directly	(max. 4 selected)	G1: F MR (50 pppm) G2: Placebo MR	None (non-F toothpaste provided)	12/ 26 wks	(Clin) Photograph	Not declared

M, male; F, female; yr, year; WSL, white spot lesion; pat, patient; CoI, conflict of interest; RCT_{SM}, split mouth randomized controlled trial; NR, not reported; G, group; F, fluoride; TP, toothpaste; ppm, parts per million; wk, week; Clin, clinical evaluation; ICDAS II, International Caries Detection and Assessment System II criteria; RCT_{PAR}, parallel randomized controlled trial; OHI, oral hygiene instructions; PTC, professional tooth cleaning; mo, month; DD, DIAGNOdent; CPP-ACP, casein phosphopeptide-stabilized amorphous calcium phosphate; NaF; sodium fluoride; MR, mouthrinse; QLF, quantitative light-induced fluorescence; USA, United States of America; EDI, Enamel Decalcification Index; CIE L*a*b, Commission internationale de l' e´ clairage Lab color space; VAS, visual analogue scale; DMFT, decayed missing filled teeth; BA, bioactive glass; UK, united kingdom.
$, additional outcomes not pertaining to WSL treatment directly are not included here.

Table 2. Results of individual studies and meta-analyses on all outcomes reported by the included studies.

Continuous outcomes									
	Comparison	n	MD	95% CI	P	tau^2	I^2	95% UI	95% PrI
Assessment VAS (expert)	$Tx_{1,2}$ vs Ctr	1*	-2.53	-11.68,6.62	0.588	-	-	-	-
Assessment VAS (layperson)	$Tx_{1,2}$ vs Ctr	1*	3.86	-4.10,11.82	0.342	-	-	-	-
Assessment VAS (objective)	$Tx_{1,2}$ vs Ctr	1*	-0.71	-7.12,5.70	0.828	-	-	-	-
Assessment VAS (self-assesment)	$Tx_{1,2}$ vs Ctr	1*	0.37	-7.22,7.96	0.924	-	-	-	-
CIE: a (WSL)	Tx_3 vs Ctr	1	-0.36	-0.77,0.05	0.086				
CIE: a (WSL) - adjusted estimate	Tx_4 vs Ctr	1	-1.45	-2.20,-0.71	<0.001				
CIE: a (WSL/SAE) - adjusted estimate	Tx_4 vs Ctr	1	-1.46	-2.03,-0.89	<0.001				
CIE: b (WSL)	Tx_3 vs Ctr	1	-5.87	-7.26,-4.48	<0.001				
CIE: b (WSL) - adjusted estimate	Tx_4 vs Ctr	1	-5.63	-7.51,-3.75	<0.001				
CIE: b (WSL/SAE) - adjusted estimate	Tx_4 vs Ctr	1	-3.65	-5.45,-1.85	<0.001				
CIE: ΔE (WSL/SAE) - adjusted estimate	Tx_4 vs Ctr	1	2.60	1.44,3.76	<0.001				
CIE: L (WSL in %)	Tx_4 vs Ctr	1	-4.50	-29.96,20.96	0.729				
CIE: L (WSL)	$Tx_{3,4}$ vs Ctr	2	1.41	-2.16,4.97	0.439	5.966	90	-	-
CIE: L (WSL) - adjusted estimate	Tx_4 vs Ctr	1	2.19	0.99,3.39	<0.001				
CIE: L (WSL/SAE) - adjusted estimate	Tx_4 vs Ctr	1	1.89	0.97,2.81	<0.001				
ΔQ (QLF)	$Tx_{2,5}$ vs Ctr	1*	12.99	7.69,18.29	<0.001	-	-	-	-
Fluoresence (QLF/DD)#	$Tx_{1,2,5\text{-}7,9,10}$ vs Ctr	8*	-0.35	-0.75,0.05	0.085	0.280	91	85,94	-1.74,1.04
ICDAS II	$Tx_{9,10}$ vs Ctr	1*	-0.66	-0.92,-0.40	<0.001	-	-	-	-
IFL (QLF)	Tx_7 vs Ctr	1	6.31	-6.40,19.02	0.331	-	-	-	-
WSL area	$Tx_{1,2,5\text{-}8}$ vs Ctr	6*	-0.48	-.98,0.01	0.056	0.235	87	71,92	-2.00,1.04
WSL area/ tooth area in %	Tx_2 vs Ctr	1	-0.66	-2.83,1.51	0.551				
Fluoresence (QLF)	Tx_7 vs Tx_{11}	1	0.00	-1.92,1.92	1.000	-	-	-	-
Binary outcomes									
Outcome	Comparison	n	OR	95% CI	P	tau^2	I^2	95% UI	95% PrI
ΔE (WSL)>3.0	Tx_3 vs Ctr	1	4.42	1.53,12.78	0.006				
ΔE (WSL)>3.7	Tx_3 vs Ctr	1	7.84	2.64,23.26	<0.001				
ΔE (WSL/Ctr)>3.0	Tx_3 vs Ctr	1	0.06	0.01,0.28	<0.001				
ΔE (WSL/Ctr)>3.7	Tx_3 vs Ctr	1	0.83	0.34,2.00	0.673				
DMFT>0	Tx_{12} vs Ctr	1	0.67	0.18,2.46	0.543				
Greater improvement than the control	Tx_4 vs Ctr	1	2.46	1.94,3.11	<0.001				
Invisible /regressed WSLs	$Tx_{7,12}$ vs Ctr	3	0.97	0.60,1.56	0.893	0.069	38	0,82	-
Invisible WSLs	Tx_7 vs Ctr	2	0.79	0.53,1.18	0.247	0	0	-	-
Nausea	$Tx_{2,5}$ vs Ctr	1*	2.43	0.09,67.57	0.601				
Regressed WSLs	Tx_7 vs Ctr	1	1.67	0.81,3.44	0.168				
Regressed WSLs (severe)	Tx_7 vs Ctr	1	2.34	1.07,5.12	0.034				
Invisible WSLs	Tx_8 vs Tx_7	1	0.16	0.08,0.35	<0.001				

N, number of included studies; MD, mean difference; CI, confidence interval; UI, uncertainty interval (confidence interval for the I^2); PrI, predictive interval (confidence interval integrating the identified heterogeneity among studies, in order to predict the possible effects in a future study); VAS, visual analogue scale; Tx, treatment (1-CPP-ACP & F; 2-F varnish; 3-Bleaching; 4-Resin infiltrant; 5-F film; 6-BG toothpaste; 7-CPP-ACP; 8-F mouthrinse; 9-F miswak; 10-Non-F miswak; 11-F toothpaste; 12-F gel); Ctr, control; CIE, Commission Internationale de l'Eclairage; WSL, white spot lesion; SAE, sound adjacent enamel; QLF, Quantitative light-induced fluorescence; DD, DIAGNOdent; ICDAS II, International Caries Detection and Assessment System II; OR, odds ratio; DMFT, decayed missing filled tooth index.

*multiple trial arms with different interventions for WSL have been pooled together.

#The Standardized Mean Difference is used instead of the Mean Difference, to account for differences in the two fluorescence measurements.

Table 3. GRADE summary of findings table for the main outcomes of the systematic review

Patients: having at least one white spot lesion on the teeth after orthodontic treatment
Settings: university clinics (China, Denmark, Germany, Netherlands, Romania, UK, USA), hospital (Saudi Arabia), and private practice (Australia)
Intervention: BG toothpaste, CPP-ACP, CPP-ACP & F, F film, F gel, F mouthrinse, F varnish, F miswak, non-F miswak
Comparison: no treatment (regular oral hygiene procedures; most with F toothpaste)

Outcomes	Illustrative comparative effects (95% CI)		Patients (trials)	GRADE*	Effect
	Control	Intervention			
Lesion area; (1.0-6.0 months)	Assumed change†	Corresponding change †	388 (6)	⊕⊕⊖⊖[a,b] Low	MD=-0.48 (-0.98,0.01); P>0.05
	Lesion shrinkage of 0.37 mm^2 for the lesions in the control groups (range 1.92 mm^2 shrinkage to 0.48 mm^2 enlargement).	The lesions shrink by 0.48 mm^2 more in the intervention groups (95% CI: 0.98 mm^2 more to 0.01 mm^2 less) than in the control groups.			
Lesion fluorescence; (1.0-6.5 months)	Assumed change†	Corresponding change	562 (8)	⊕⊕⊖⊖[a,b] Low	SMD=-0.35 (-0.75,0.05); P>0.05
	The enamel fluorescence increases by 1.07% in the control groups (range 0.80% to 3.67% increase).	The enamel fluorescence increases by 0.88% more in the intervention groups (1.88% more to 0.13% less) than in the control groups.			
Improvement/regression of the lesion's clinical assessment (3.0-6.0 months)	Assumed risk per 1000 lesions†	Corresponding risk per 1000 lesions	144 (3)	⊕⊕⊕⊖[b] moderate	OR=0.97 (0.60,1.56); P>0.05
	587 lesions per 1000 regress in the control groups.	17 lesions fewer per 1000 (235 less to 329 more) regress compared to the intervention groups.			

BG, bioactive glass; CPP-ACP, casein phosphopeptide-stabilized amorphous calcium phosphate; F, fluoride; CI, confidence interval; MD, mean difference; SMD, standardized mean difference; OR, odds ratio.
†Assumed changes and risks adopted from the randomized trials of He *et al.* (37) and Bailey *et al.* (38) , respectively, which were judged to be the most robust.
*All GRADE scores start from high, due to the inclusion of randomized trials.
[a] Downgraded by one for heterogeneity.
[b] Downgraded by one for imprecision.

Supplementary material

Interventions for orthodontically-induced white spot lesions: a systematic review and meta-analysis

Supplementary material 1. Inclusion/exclusion criteria for this systematic review (as initially planned in the protocol; the included outcomes were reviewed *post hoc*).

Domain	Inclusion	Exclusion
Participants	▪ Human patients ▪ Patients of any age/sex/ethnicity with at least one white spot lesion on the labial or lingual surface of the teeth induced by a previous treatment with orthodontic appliances	▪ Animal studies
Interventions	▪ Any treatment	-
Comparisons	▪ No treatment ▪ Any other kind of treatment	-
Outcome	▪ (primary): color difference (WSL vs adjacent sound enamel) between the treatment and the control groups ▪ Segregated tooth color parameters L, a, b ▪ Lesion severity ▪ Lesion transition (progression, stability or regression) ▪ Lesion depth ▪ Lesion area ▪ Integrated fluorescence loss	-
Study design	▪ Randomized controlled trials (parallel or clustered) ▪ Quasi-randomized controlled trials (parallel or clustered)	▪ Non-randomized prospective or retrospective studies ▪ Case reports/ case series ▪ Non-clinical studies (in vitro, ex vivo, in silico, etc) ▪ Systematic reviews (after checked for studies)

Supplementary material 2. Literature databases searched with search strategy and yield (last search May 9, 2016).

Database	Site	Search strategy	Limit	Hits
PubMed	http://www.ncbi.nlm.nih.gov/pubmed/	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries")	Randomized Controlled Trial; Humans	86
Cochrane Library (CDSR)	http://onlinelibrary.wiley.com/cochranelibrary/search/	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries")	-	6
Cochrane Library (DARE)	http://onlinelibrary.wiley.com/cochranelibrary/search/	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries")	-	6
Cochrane Library (CENTRAL)	http://onlinelibrary.wiley.com/cochranelibrary/search/	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries") AND random*	-	223
Virtual Health Library	http://pesquisa.bvsalud.org/portal/advanced/?lang=en	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries") AND random*	-	9
Scopus	http://www.scopus.com/	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries") AND random*	Dentistry	67
ISI Web of Knowledge	http://apps.webofknowledge.com	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries") AND random*	Research area: dentistry oral surgery medicine Document type: clinical trial	192
ClinicalTrials.gov	https://clinicaltrials.gov/	("fixed appliance" OR orthodon* OR "fixed orthodontic" OR bracket* OR multibracket) AND (reminerali* OR deminerali* OR decalcif* OR "white spot" OR "white spot lesion" OR "enamel" OR enamel surface* "caries")	-	11
Overall				594

Supplementary material 3. List of included and excluded studies, with the corresponding reasons.

No	Paper	
	Exclusion by title	
1	[No authors included] {NCT00268138} Elmex Gel Efficacy in Preventing White Spot Lesions. Status: Unknown.	Exclude by title.
2	[No authors included] {NCT01082822} Periodontal Ligament Stem Cell Implantation in the Treatment of Periodontitis. Status: Unknown.	Exclude by title.
3	Agrawal A, Shigli A. Comparison of six different methods of cleaning and preparing occlusal fissure surface before placement of pit and fissure sealant: an in vitro study. Journal of the Indian Society of Pedodontics and Preventive Dentistry. 2012;30(1):51-5.	Exclude by title.
4	Al Shamsi A, Cunningham JL, Lamey PJ, Lynch E. Shear bond strength and residual adhesive after orthodontic bracket debonding. The Angle orthodontist 2006; (4):694-9.	Exclude by title.
5	Al Shamsi AH, Cunningham JL, Lamey PJ, Lynch E. The effects of ozone gas application on shear bond strength of orthodontic brackets to enamel. American journal of dentistry 2008; (1):35-8.	Exclude by title.
6	Al-Twaijri S, Viana G, Bedran-Russo AK. Effect of prophylactic pastes containing active ingredients on the enamel-bracket bond strength of etch-and-rinse and self-etching systems. The Angle orthodontist 2011; (5):788-93.	Exclude by title.
7	Atsü SS, Gelgör IE, Sahin V. Effects of silica coating and silane surface conditioning on the bond strength of metal and ceramic brackets to enamel. The Angle orthodontist 2006; (5):857-62.	Exclude by title.
8	Attar N, Korkmaz Y, Kilical Y, Saglam-Aydinatay B, Bicer CO. Bond strength of orthodontic brackets bonded to enamel with a self-etching primer after bleaching and desensitizer application. Korean Journal of Orthodontics 2010; (5):342-8.	Exclude by title.
9	Baumann DF, Brauchli L, Waes H. The influence of dental loupes on the quality of adhesive removal in orthodontic debonding. J Orthofac Orthop 2011; (2):125-32.	Exclude by title.
10	Baysal A, Uysal T. Do enamel microabrasion and casein phosphopeptide-amorphous calcium phosphate affect shear bond strength of orthodontic brackets bonded to a demineralized enamel surface? Angle Orthod 2012;82(1):36-41.	Exclude by title.
11	Bazargani F, Jacobson S, Lennartsson B. A comparative evaluation of lingual retainer failure bonded with or without liquid resin. The Angle orthodontist 2012; (1):84-7.	Exclude by title.
12	Behnan SM, Arruda AO, Gonzalez-Cabezas C, Sohn W, Peters MC. In-vitro evaluation of various treatments to prevent demineralization next to orthodontic brackets. Am J Orthod Dentofac Orthop 2010;138(6):712 e1-7.	Exclude by title.
13	Bishara SE, Ajlouni R, Oonsombat C, Laffoon J. Bonding orthodontic brackets to porcelain using different adhesives/enamel conditioners: a comparative study. World journal of orthodontics 2005; (1):17-24.	Exclude by title.
14	Bishara SE, Damon PL, Olsen ME, Jakobsen JR. Effect of applying chlorhexidine antibacterial agent on the shear bond strength of orthodontic brackets. The Angle orthodontist 1996; (4):313-6.	Exclude by title.
15	Bishara SE, Ostby AW, Ajlouni R, Laffoon JF, Warren JJ. Early shear bond strength of a one-step self-adhesive on orthodontic brackets. The Angle orthodontist 2006; (4):689-93.	Exclude by title.
16	Bishara SE, Ostby AW, Laffoon J, Warren JJ. Enamel cracks and ceramic bracket failure during debonding in vitro. The Angle orthodontist 2008; (6):1078-83.	Exclude by title.
17	Bishara SE, Ostby AW, Laffoon JF, Warren J. Shear bond strength comparison of two adhesive systems following thermocycling. A new self-etch primer and a resin-modified glass ionomer. The Angle orthodontist 2007; (2):337-41.	Exclude by title.
18	Bishara SE, Ostby AW, Laffoon JF, Warren JJ. The effect of modifying the self-etchant bonding protocol on the shear bond strength of orthodontic brackets. The Angle orthodontist 2007; (3):504-8.	Exclude by title.
19	Bishara SE, Soliman M, Ajlouni R, Laffoon J, Warren JJ. Waterline disinfectant effect on the shear bond strength of orthodontic brackets. The Angle orthodontist 2005; (6):1032-5.	Exclude by title.
20	Bishara SE, Soliman M, Laffoon J, Warren JJ. Effect of antimicrobial monomer-containing adhesive on shear bond strength of orthodontic brackets. The Angle orthodontist 2005; (3):397-9.	Exclude by title.
21	Bishara SE, Soliman M, Laffoon JF, Warren J. Shear bond strength of a new high fluoride release glass Ionomer adhesive. Angle Orthod 2008;78(1):125-8.	Exclude by title.
22	Bokle D, Munir H. An in vitro study of the effect of Pro Seal varnish on the shear bond strength of orthodontic brackets. World journal of orthodontics 2008; (2):141-6.	Exclude by title.
23	Borges AFS, Simonato LE, Pascon FM, Kantowitz KR, Rontani RMP. Effects of resin luting agents and 1 percent NaOCl on the marginal fit of indirect composite restorations in primary teeth. J appl oral sci.19(5):455-61.	Exclude by title.
24	Brackett MG, Dib A, Brackett WW, Estrada BE, Reyes AA. One-year clinical performance of a resin-modified glass ionomer and a resin composite restorative material in unprepared Class V restorations. Operative dentistry. 2002;27(2):112-6. Epub 2002/04/05.	Exclude by title.
25	Brackett WW, Dib A, Brackett MG, Reyes AA, Estrada BE. Two-year clinical performance of Class V resin-modified glass-Ionomer and resin composite restorations. Operative dentistry. 2003;28(5):477-81.	Exclude by title.
26	Cal-Neto JP, Carvalho F, Almeida RC, Miguel JA. Evaluation of a new self-etching primer on bracket bond strength in vitro. The Angle orthodontist 2006; (3):466-9.	Exclude by title.
27	Cal-Neto JP, Miguel JA, Zanella E. Effect of a self-etching primer on shear bond strength of adhesive precoated brackets in vivo. The Angle orthodontist 2006; (1):127-31.	Exclude by title.
28	Canay S, Kocadereli I, Ak"ca E. The effect of enamel air abrasion on the retention of bonded metallic orthodontic brackets. Am J Orthod Dentofac Orthop 2000; (1):15-9.	Exclude by title.
29	Carstensen W. Effect of Reduction of Phosphoric-Acid Concentration on the Shear Bond Strength of Brackets. Am J Orthod Dentofac Orthop 1995;108(3):274-7.	Exclude by title.
30	Cehreli SB, Sar C, Polat-Özsoy O, Unver B, Ozsoy S. Effects of a fluoride-containing casein phosphopeptide-amorphous calcium phosphate complex on the shear bond strength of orthodontic brackets. Eur J Orthod 2012; (2):193-7.	Exclude by title.
31	Chan DC, Browning WD, Frazier KB, Brackett MG. Clinical evaluation of the soft-start (pulse-delay) polymerization technique in Class I and II composite restorations. Operative dentistry. 2008;33(3):265-71. Epub 2008/05/29.	Exclude by title.
32	Chen DR, McGorray SP, Dolce C, Wheeler TT. Effect of early Class II treatment on the incidence of incisor trauma.	Exclude by title.

	Am J Orthod Dentofac Orthop 2011; (4):e155-60.	
33	Cheng HY, Chen CH, Li CL, Tsai HH, Chou TH, Wang WN. Bond strength of orthodontic light-cured resin-modified glass ionomer cement. Eur J Orthod 2011; (2):180-4.	Exclude by title.
34	Chicri RO, Sasaki RT, Carvalho AS, Nouer PR, Lima-Arsati YB. Effect of enamel pretreatment on shear bond strength of brackets bonded with resin-modified glass-ionomer cement. World journal of orthodontics 2010; (1):11-5.	Exclude by title.
35	Cho JY, Lee DY, Lim YK. Shear bond strength of orthodontic adhesive to amalgam surface using light-cured resin. Korean Journal of Orthodontics 2005; (6):443-50.	Exclude by title.
36	Compton AM, Meyers CE, Hondrum SO, Lorton L. Comparison of the shear bond strength of a light-cured glass ionomer and a chemically cured glass ionomer for use as an orthodontic bonding agent. Am J Orthod Dentofac Orthop 1992; (2):138-44.	Exclude by title.
37	Cucu M, Driessen CH, Ferreira PD. The influence of orthodontic bracket base diameter and mesh size on bond strength. SADJ : journal of the South African Dental Association = tydskrif van die Suid-Afrikaanse Tandheelkundige Vereniging 2002; (1):16-20.	Exclude by title.
38	Danaei SM, Safavi A, Roeinpeikar SM, Oshagh M, Iranpour S, Omidkhoda M, et al. Ion release from orthodontic brackets in 3 mouthwashes: an in-vitro study. Am J Orthod Dentofac Orthop 2011; (6):730-4.	Exclude by title.
39	Davari A, Yassaei S, Karandish M, Zarghami F. In vitro evaluation of microleakage under ceramic and metal brackets bonded with LED and plasma arc curing. The journal of contemporary dental practice 2012; (5):644-9.	Exclude by title.
40	Davidovitch M, Efstathiou S, Sarne O, Vardimon AD. Skeletal and dental response to rapid maxillary expansion with 2- versus 4-band appliances. Am J Orthod Dentofac Orthop 2005; (4):483-92.	Exclude by title.
41	Dubernard C, Raynal P, Tramini P. Comparative study of enamel adhesion between RelyX Unicem (3M), a self-adhesive bonding agent, and the combination of MIP (3M), a hydrophilic adhesive, and Transbond Supreme Low Viscosity (3M), a traditional hydrophobic adhesive. International Orthodontics 2013; (3):247-61.	Exclude by title.
42	El-Angbawi A, McIntyre Grant T, Fleming Padhraig S, Bearn David R. Non-surgical adjunctive interventions for accelerating tooth movement in patients undergoing fixed orthodontic treatment. Cochrane Database of Systematic Reviews 2015; (11).	Exclude by title.
43	Farhadian N, Usefi Mashoof R, Khanizadeh S, Ghaderi E, Farhadian M, Miresmaeili A. Streptococcus mutans counts in patients wearing removable retainers with silver nanoparticles vs those wearing conventional retainers: A randomized clinical trial. Am J Orthod Dentofac Orthop 2016;149(2):155-60.	Exclude by title.
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46	Forsberg CM, Hagberg C. Shear bond strength of ceramic brackets with chemical or mechanical retention. British journal of orthodontics 1992; (3):183-9.	Exclude by title.
47	Germeç D, Taner TU. Effects of extraction and nonextraction therapy with air-rotor stripping on facial esthetics in postadolescent borderline patients. Am J Orthod Dentofac Orthop 2008; (4):539-49.	Exclude by title.
48	Gilpatrick RO, Johnson W, Moore D, Turner J. Pulpal response to dentin etched with 10% phosphoric acid. American journal of dentistry 1996; (3):125-9.	Exclude by title.
49	Gomes P, Portugal J, Jardim L. Effect of high-powered LED-curing exposure time on orthodontic bracket shear bond strength. Revista Portuguesa de Estomatologia, Medicina Dentaria e Cirurgia Maxilofacial 2014; (2):78-82.	Exclude by title.
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51	Goracci C, Gheewalla R, Kugel G, Ferrari M. Orthodontic-restorative treatment of chipped or worn incisors. American journal of dentistry 2001; (1):50-5.	Exclude by title.
52	Goracci C, Margvelashvili M, Giovannetti A, Vichi A, Ferrari M. Shear bond strength of orthodontic brackets bonded with a new self-adhering flowable resin composite. Clinical oral investigations 2013; (2):609-17.	Exclude by title.
53	Gungor AY, Ozcan E, Alkis H, Turkkahraman H. Effects of different bleaching methods on shear bond strengths of orthodontic brackets. The Angle orthodontist 2013; (4):686-90.	Exclude by title.
54	Hammad SM, Enan ET. In vivo effects of two acidic soft drinks on shear bond strength of metal orthodontic brackets with and without resin infiltration treatment. The Angle orthodontist 2013; (4):648-52.	Exclude by title.
55	Harris AMP, Joseph VP, Rossouw PE. Shear Peel Bond Strengths of Aesthetic Orthodontic Brackets. Am J Orthod Dentofac Orthop 1992;102(3):215-9.	Exclude by title.
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57	Ireland AJ, Soro V, Sprague SV, Harradine NW, Day C, Al-Anezi S, et al. The effects of different orthodontic appliances upon microbial communities. Orthodontics & craniofacial research 2014; (2):115-23.	Exclude by title.
58	Isci D, Sahin Saglam AM, Alkis H, Elekdag-Turk S, Turk T. Effects of fluorosis on the shear bond strength of orthodontic brackets bonded with a self-etching primer. Eur J Orthod 2011; (2):161-6.	Exclude by title.
59	Jia H, Zhu XY. Effect of three bonding adhesives on the orthodontic bracket loss rate in treating moderate and severe dental fluorosis. [Chinese]. Journal of Clinical Rehabilitative Tissue Engineering Research 2010; (16):2925-8.	Exclude by title.
60	Kim YK, Lee JW, Cha KS. A comparative study on bond strength and adhesive failure pattern in bracket bonding with self-etching primer. Korean Journal of Orthodontics 2004; (4):325-32.	Exclude by title.
61	Koch G, Hakeberg M, Petersson LG. Fluoride Uptake on Dry Versus Water-Saliva Wetted Human-Enamel Surfaces Invitro after Topical Application of a Varnish (Duraphat) Containing Fluoride. Swedish dental journal. 1988;12(6):221-5.	Exclude by title.
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63	Koroluk LD, Tulloch JF, Phillips C. Incisor trauma and early treatment for Class II Division 1 malocclusion. Am J Orthod Dentofac Orthop 2003; (2):117-25; discussion 25-6.	Exclude by title.
64	Kraut J, Radin S, Trowbridge HI, Emling RC, Yankell SL. Clinical evaluations on thermal versus mechanical debonding of ceramic brackets. The Journal of clinical dentistry 1991; (4):92-6.	Exclude by title.

65	Kuramoto M, Jr., Matos AB, Matson E, Eduardo CP, Powers JM. Microleakage of resin-based composite restorations with ceramic inserts. American journal of dentistry. 2000;13(6):311-4. Epub 2002/01/05.	Exclude by title.
66	Lamper T, Steinhäuser-Andresen S, Huth KC, Ilie N, Paschos E. Does a reduction of polymerization time and bonding steps affect the bond strength of brackets? Clinical oral investigations 2012; (2):665-71.	Exclude by title.
67	Le T, Nassery K, Kahlert B, Heithersay G. A comparative diagnostic assessment of anterior tooth and bone status using panoramic and periapical radiography. Australian orthodontic journal 2011; (2):162-8.	Exclude by title.
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69	Lombardo L, Bulli C, Mirabella D, Bonetti AG, Siciliani G. Comparison of adhesion forces developed by foil mesh of various dimensions applied in combination with composites of different viscosity. International Orthodontics 2013; (3):290-302.	Exclude by title.
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71	Magnius M, Bazargani F. Effects of oil-based and oil-free enamel prophylactic agents on bracket failure--a prospective randomized clinical trial. Swedish dental journal 2014; (2):87-91.	Exclude by title.
72	Mahdavie NN, Manasse RJ, Viana G, Evans CA, Bedran-Russo AB. Enamel scarring by debonding burs: an SEM and profilometric study. Journal of clinical orthodontics : JCO 2014; (1):14-21.	Exclude by title.
73	Mayne RJ, Cochrane NJ, Cai F, Woods MG, Reynolds EC. In-vitro study of the effect of casein phosphopeptide amorphous calcium fluoride phosphate on iatrogenic damage to enamel during orthodontic adhesive removal. Am J Orthod Dentofac Orthop 2011;139(6):e543-51. Epub 2011/06/07.	Exclude by title.
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75	Millett Declan T, Mandall Nicky A, Mattick Rye CR, Hickman J, Glenny A-M. Adhesives for bonded molar tubes during fixed brace treatment. Cochrane Database of Systematic Reviews 2011; (6).	Exclude by title.
76	Millett DT, Doubleday B, Alatsaris M, Love J, Wood D, Luther F, et al. Chlorhexidine-modified glass ionomer for band cementation? An in vitro study. Journal of orthodontics. 2005;32(1):36-42. Epub 2005/03/24.	Exclude by title.
77	Mirabella D, Spena R, Scognamiglio G, Luca L, Gracco A, Siciliani G. LED vs halogen light-curing of adhesive-precoated brackets. The Angle orthodontist 2008; (5):935-40.	Exclude by title.
78	Mitchell L (1992) Decalcification during orthodontic treatment with fixed appliances—an overview. Br J Orthod 19:199–205	Exclude by title.
79	Murfitt PG, Quick AN, Swain MV, Herbison GP. A randomised clinical trial to investigate bond failure rates using a self-etching primer. Eur J Orthod 2006; (5):444-9.	Exclude by title.
80	Nandhra SS, Littlewood SJ, Houghton N, Luther F, Prabhu J, Munyombwe T, et al. Do we need primer for orthodontic bonding? A randomized controlled trial. Eur J Orthod 2015; (2):147-55.	Exclude by title.
81	Noel L, Rebellato J, Sheats RD. The effect of argon laser irradiation on demineralization resistance of human enamel adjacent to orthodontic brackets: an in vitro study. Angle Orthod 2003;73(3):249-58. Epub 2003/06/28.	Exclude by title.
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83	Ogihara S, Wang HL. Periodontal regeneration with or without limited orthodontics for the treatment of 2- or 3-wall infrabony defects. Journal of periodontology 2010; (12):1734-42.	Exclude by title.
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87	Oskoee SS, Oskoee PA, Navimipour EJ, Shahi S. In vitro fracture resistance of endodontically-treated maxillary premolars. Operative dentistry 2007; (5):510-4.	Exclude by title.
88	Osorio R, Toledano M, Garcia-Godoy F. Bracket bonding with 15- or 60-second etching and adhesive remaining on enamel after debonding. The Angle orthodontist 1999; (1):45-8.	Exclude by title.
89	Ostby AW, Bishara SE, Laffoon J, Warren JJ. Influence of self-etchant application time on bracket shear bond strength. The Angle orthodontist 2007; (5):885-9.	Exclude by title.
90	Ovrebo RC, Raadal M. Microleakage in fissures sealed with resin or glass ionomer cement. Scandinavian journal of dental research. 1990;98(1):66-9. Epub 1990/02/01.	Exclude by title.
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92	Park SB, Kang EH, Son WS, Ko CC, Kim HI, Kwon YH. Effect of DPSS laser on the shear bond strength of orthodontic brackets. American journal of dentistry 2010; (4):205-7.	Exclude by title.
93	Pellegrini P, Sauerwein R, Finlayson T, McLeod J, Covell DA, Maier T, et al. Plaque retention by self-ligating vs elastomeric orthodontic brackets: quantitative comparison of oral bacteria and detection with adenosine triphosphate-driven bioluminescence. Am J Orthod Dentofac Orthop 2009; (4):426.e1-9; discussion -7.	Exclude by title.
94	Peng Y, Wu R, Qu W, Wu W, Chen J, Fang J, et al. Effect of visual method vs plaque disclosure in enhancing oral hygiene in adolescents and young adults: a single-blind randomized controlled trial. Am J Orthod Dentofac Orthop 2014; (3):280-6.	Exclude by title.
95	Perdigao J, Gomes G, Gondo R, Fundingsland JW. In vitro bonding performance of all-in-one adhesives. Part I - Microtensile bond strengths. Journal of Adhesive Dentistry. 2006;8(6):367-73.	Exclude by title.
96	Perez-Lajarin L, Cortes-Lillo O, Garcia-Ballesta C, Cozar-Hidalgo A. Marginal microleakage of two fissure sealants: a comparative study. Journal of dentistry for children (Chicago, Ill). 2003;70(1):24-8. Epub 2003/05/24.	Exclude by title.

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303	[No authors included] {NCT01329731} Remineralisation of White Spot Lesions by Elmex® gelée in Post-orthodontic Patients. Status: Completed.	Exclude by fulltext; trial registered and completed, but not yet published; no response from trialists.
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331	Shell ER. Effectiveness of Mi PasteTM, Mi Paste PlusTM, and Topex RenewTM in remineralization and visible reduction of white spot lesions after orthodontic treatment - a clinical study. Master thesis, University of Iowa, 2012.	Included
332	Willmot DR. White lesions after orthodontic treatment: does low fluoride make a difference? Journal of orthodontics. 2004;31(3):235-42.	Included

WSL, white spot lesion; ortho-Tx, orthodontic treatment.

Supplementary material 4. Detailed risk of bias assessment for the included trials.

AA	Trial	Sequence generation	Allocation concealment	Blinding of participants/ personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
1	Agarwal 2013	**Unclear** – "…in a double-blind, randomized, longitudinal trial…"	**Unclear** – No mention throughout the paper.	**Unclear** – the trial is described as double-blind, but no effective blinding measure is described.	**High risk** – no mention of blinding throughout the paper; blinding should be possible.	**Low risk** – No drop-outs or patient losses are reported	**High risk** – It is difficult to judge whether selective reporting is a problem, as no protocol exists; however, no data is adequately reported in the published report.	**Unclear** – intervention is self-administered by the patient and compliance with the instructions not assessed in the study; additionally, it is not clear whether clustering of measurements has been adequately assessed in the analyses.
2	Aljehani 2006	**Low risk** - „The subjects were randomly assigned to one of the two groups by using a random number table"	**Unclear** – No mention throughout the paper.	**Unclear** - Blinding is feasible for patients/orthodontist; both objective and subjective outcomes are included and blindly not adequately described as blind for all cases: „The subjects and the dental assistant were aware of the group assignment, which was unavailable to the examiner".	**Unclear** –„The subjects and the dental assistant were aware of the group assignment, which was unavailable to the examiner"; however, blinding is not completely described, while both subjective and objective outcomes are included.	**Low risk** - No drop-outs or patient losses are reported.	**High risk** – It is difficult to judge whether selective reporting is a problem, as no protocol exists; however, no data is adequately reported in the published report.	**Unclear** – intervention is self-administered by the patient and compliance with the instructions not assessed in the study.
3	Anderss on 2007	**Low risk** - „The patients were randomly assigned with a dice to one of two 6-month treatment regimes"	**Unclear** – No mention throughout the paper.	**Unclear** - Blinding was feasible for patients/orthodontist; outcome is objective and assessed blindly.	**Low risk** - Blinding of outcome assessor: "The clinical recordings were performed by one blinded examiner (AA) who was calibrated before the start of the study. The examiner could not see the previous registered clinical scores or LF values at the follow-up sessions".	**Low risk** - „One male in group B was lost during follow-up due to relocation": one drop-out, which was considered to be random and minor.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**High risk** – intervention is self-administered by the patient, but compliance with the instructions was assessed in the study and considered similar in the two groups; however, clustering of measurements has been disregarded in the analyses; additionally, the one intervention was used for the half of the study period (3 mos), while the second was used for the whole period (6 mos).
4	Baeshe n 2011	**Low risk** - „The participants were randomly divided based on a randomization list into 2 groups".	**Unclear** – No mention throughout the paper.	**Unclear** – "The participants and the examiner were not aware of the group assignments, not even the covered or noncovered side": blinding of the personell and patient could be performed as intervention is self-administered and the two miswaks were	**Low risk** – blinding of outcome assessors was undertaken (see previous domain).	**Low risk** - No drop-outs or patient losses are reported.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**High risk** – intervention is self-administered by the patient and compliance with the instructions not assessed in the study; additionally, clustering of measurements has been disregarded in the analyses.

				identical: "The 2 types of miswaks were identical except for their fluoride content"; however, only blinding of the participants was undertaken.				
5	Bailey 2009	**Low risk** – "The paricipants were allocated to one of the two study products, according to a computer-generated random permuted blocks schedule (blocks of four and six)".	**Low risk** – central allocation: "blinded product packages prepared by non-clinical staff labeled with a 3-digit code and visit number, study products were supplied in identical packaging with no observable difference in appearance, taste or smell".	**Low risk** – complete blinding feasible and undertaken; see allocation concealment text.	**Low risk** – complete blinding feasible and undertaken; see allocation concealment text; also "The randomization schedule was secured and released only upon completion of all data collection and database lock".	**Low risk** – all randomized patients were analyzed at the final timepoint; minor drop-outs for intermediate time-points were negligible.	**Low risk** – trial has been registered in ANZCTR and although some minor points exist (outcome measurement procedure changes during trial due to technique sensitivity; retrospective registration), the risk of bias was judged as low.	**Low risk** – intervention is self-administered by the patient, but compliance with the instructions was assessed in the study: "Product tubes were weighed prior to dispensation and on return from the participant. Overall compliance was calculated as the total amount of study product used"; clustering of measurements has been taken into account in the analyses.
6	Beerens 2010	**Low risk** - Subjects, complying with the inclusion criteria determined by M.W.B., were then randomly assigned by M.H.V. to either the CPP-ACFP group or the control group, as determined by a computer-randomization scheme that was created and locked before the start of the study.	**Unclear** – allocation concealment unclear; not clear how the person randomizing patients (MHV) was involved in the study, although she probably did not have to do anything with the clinical procedures.	**Low risk** - double-blind; complete blinding feasible and undertaken; „The subjects received neutral-coloured toothpaste tubes marked A or B, which contained either CPP-ACP + sodium fluoride".	**Low risk** – "The images were captured by several examiners who were calibrated before the start of the investigation and who were blinded with respect to the treatment group …..The QLF images obtained for each subject were analysed blind with regard to treatment group; the group allocations were added to the exported data after completion of all analyses".	**Unclear** - "a total of ten participants dropped out between T0 and T3, seven from the CPP-ACFP group and three from the control group. The reason given for withdrawal was the time-consuming nature of the study. One further participant from the CPP-ACFP group was found to be WSL free and was removed from the study. These participants did not differ with respect to number of lesions, gender ratio, age, and MB treatment duration compared with subjects who completed the study.": a small-to-moderate number of patients (15%) left the study; although the authors report that the reasons didn't have to do with the allocated group,	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Low risk** – intervention is self-administered by the patient, but compliance with the instructions was assessed in the study: "Compliance was checked by questions asked on each visit about the frequency of tooth brushing and application of the study paste and how often, and when these were forgotten. Furthermore, subjects were asked to bring their study paste on each visit."; clustering of measurements has been taken into account in the analyses.

						the dropped patients were not equally distributed in groups and no formal analysis was reported.		
7	Brochner 2011	**Low risk** – "The subjects were allocated to one of the two groups as determined with aid of computer randomization".	**Unclear** – No mention throughout the paper.	**High risk** - Blinding was feasible for patients/orthodontist, but was not undertaken/described.	**Low risk** – "The researchers responsible for the study and evaluating the endpoints were not involved in the clinical work and blinded for the group assignment": although blinding not completely described, it was judged as adequate.	**High risk** – "It should also be stressed that the dropout numbers were comparatively high (20–25%) also for the visual readings due to technical problems. "	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Low risk** – intervention is self-administered by the patient, but compliance with the instructions was assessed in the study: "Based on the personal interviews, we had all reasons to believe that the subjects complied with the study protocol"; clustering of measurements has been taken into account in the analyses.
8	Clark 2011	**High risk** – allocation method not truly random: "The first six patients who met the study criteria were selected for the treatment group. The following six patients who again met the study criteria were selected to be the control subjects".	**Unclear** – No mention throughout the paper.	**High risk** - Blinding was feasible for patients/orthodontist, but was not undertaken/described.	**High risk** – no mention of blinding throughout the paper; blinding should be possible.	**Low risk** – No drop-outs are being reported.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**High risk** – intervention is self-administered by the patient and compliance with the instructions not assessed in the study; additionally, clustering of measurements has been disregarded in the analyses.
9	Cronan 2012	**Unclear** – "Treatment and control sides were divided up by randomly assigning patients to either the right or left side treatment group upon enrollment in the study."	**Unclear** – No mention throughout the paper	**Unclear** – no mention of patients'/orthodontists' blinding throughout the paper; blinding is impractical for the clinician, but should be possible for the patient.	**Low risk** – "All lesions were scored by a single examiner who was blinded to timepoint and group assignment": description vague, but blinding was judged to be possible correctly used.	**Low risk** – No drop-outs or patient losses are reported	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – intervention is administered by the clinician, so compliance is not a problem; however, it is not clear if additional bias could have been introduced by the inclusion of patients that had been debonded during the last 0.5-14 years (in these patients, an initial remineralization through saliva and fluoride toothpaste has already taken place)—although this was attemped to be controlled for in the analyses (cut-off of 4 months), the intervention might not work the same in fresh and old WSLs; additionally, it is not clear whether clustering of measurements has been adequately assessed in the

								analyses (unclear GEE analysis description); finally considerably more WSL exist than other studies and no explanation is given for this.
10	Du 2012	**Low risk** – "Using a random number table, the participants were assigned to either the test group or the placebo group".	**Low risk** – "Randomization was performed by a researcher not involved in the study".	**Unclear** – no mention of patients'/orthodontists' blinding throughout the paper; blinding is impractical for the clinician, but should be possible for the patient; although not explicitly stated, the use of saline solution for the control group indicates a possible degree of blinding.	**Low risk** – "The assessments in all visits were carried out by the same dentist who was blind as to group allocation of the subjects".	**Unclear** – 14 (13%) dropouts; due to harsh criteria ("subjects who missed one or more visits were regarded as dropout (non-compliant patients"). No description given about the allocation of the drop-outs and no assessment in the analysis of this factor.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – intervention is administered by the clinician, so compliance is not a problem; however, clustering of measurements has been disregarded in the analyses.
11	Eckstein 2013; Knosel 2013; Eckstein 2015	**Low risk** – "Simple randomized cluster (quadrant) allocation was performed by lot before the start of the trial by the second author."	**Low risk** – "the allocations were concealed in opaque envelopes (lots) by a person not connected with this study."	**Unclear** - Blinding is impractical for both patients and clinician; outcome is objective, but was not assessed blindly.	**High risk** – "there was no blinding of the assessor to the intervention or the control quadrants."	**Low risk** – minor dropouts: "One droupout because of missing to four appointments".	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – intervention is administered by the clinician, so compliance is not a problem; additionally, clustering of measurements is not an issue; however, it is not clear if additional bias could have been introduced by the inclusion of patients that had been debonded between 1-12 months before (mean 5.1 months; in patients with a considerable elapsed time, an initial remineralization through saliva and fluoride toothpaste has taken place); additionally,it is not clear whether analyses were performed after commencement and before completion ("Sample size calculation (…) based on completed assessment cycles of the first 13 subjects indicated that 20 subjects (each with a mean of 8.3 trial teeth)"; which could introduce bias.
12	He 2016	**Low risk** – "Randomization was accomplished using Excel (Microsoft) software for simple randomization.".	**Low risk** – "After the schedule was made, group assignment information was written on cards and concealed in nontransparent envelopes with	**Unclear** - Blinding is impractical for both patients and clinician; however, outcome is objective and assessed blindly.	**Low risk** – "Additionally, the examiners who conducted the imaging acquisition and the analysis of the images were blinded to the intervention allocation… a unique subject identifier was allocated…"	**Low risk** – Minor drop-outs and full data are given about the characteristics of the drop-outs.	**Low risk** – trial protocol registered prospectively and available online. No considerable changes to the protocol were found (also "No changes were	**Low risk** – intervention is administered by the clinician, so compliance is not a problem; additionally, clustering of measurements is not an issue.

			sequential numbers on the outside to achieve allocation concealment. The generation of a random allocation sequence and the preparation of the cards and envelopes were finished well before patient recruitment by an author (Y.Z.).”				made after trial commencement)”.	
13	Huang 2013	**Low risk** – “The randomization sequence was created by using statistical software (axio research) and was stratified by each office by using random block sizes of 3 and 6.”	**Low risk** – Allocation sequence was concealed from the office during enrollment. To receive the patient’s treatment assignment the NW PRECEDENT office phoned Axio Research.	**Unclear** - Blinding is impractical for both patients and clinician; however, outcome is objective and assessed blindly.	**Low risk** – “Two panels consisting of 5 dental professionals and 5 laypersons assessed the before-and-after pairs of photographs in a blinded fashion” and “Two blinded examiners performed the objective assessment of the WSLs. The outcome assessors and the study investigators were kept blinded to the study arms until completion of the statistical analyses”	**Low risk** – “Twenty participants withdrew or were lost to follow-up between the start and the end of the study, including 11 from the MI Paste Plus group, 2 from the PreviDent group, and 7 from the home-care control group. They did not vary with respect to demographic data and initial WSL severity compared with the subjects who completed the study.”.	**Low risk** – trial protocol registered prospectively and available online. No considerable changes to the protocol were found.	**Unclear** – intervention is either administered by the clinician, so compliance is not a problem or it compliance has been assessed (“Compliance was checked by questions at the follow-up visit about the frequency of application of the MI Paste Plus.”); additionally, clustering of measurements is not an issue; however, it is not clear if additional bias could have been introduced by the inclusion of patients that had been debonded during the last two months (in these patients, an initial remineralization through saliva and fluoride toothpaste has taken place).
14	Jumanca 2012	**Unclear** – “The remaining 60 patients, were randomly divided in 3 groups and received different therapeutic conduct, as follows:..”	**Unclear** – No mention throughout the paper.	**Unclear** – no mention of blinding throughout the paper; blinding is impractical for both patient and clinician.	**High risk** – no mention of blinding throughout the paper; blinding should be possible	**High risk** – Two drop-outs caused by too high DiagnoDent pen values; the number of drop-outs is per se small, but the justification is inappropriate.	**High risk** – It is difficult to judge whether selective reporting is a problem, as no protocol exists; however, patient satisfaction is mentioned on page 785, but no further data are given; additionally, results about randomized group 3 are not given at all.	**Unclear** – intervention is administered by the clinician, so compliance is not a problem however it is not clear if clustering of measurements is an issue; furthermore, several important information of the trial (including results of a randomized group) are missing.
15	Knosel 2007	**Unclear** – “Nineteen patients with inactive WSLs after therapy	**Unclear** – No mention throughout the paper.	**Unclear** - Blinding is impractical for both patients and clinician;	**High risk** – no mention of blinding throughout the paper; blinding should be	**Low risk** – No drop-outs or patient losses are reported	**High risk** – It is difficult to judge whether selective	**Unclear** – intervention is administered by the clinician, so compliance is not a problem;

		with fixed orthodontic appliances were selected and randomly placed into two groups".		however, outcome is objective and assessed blindly.	possible. All determinations were performed by the same operator.		reporting is a problem, as no protocol exists; results of at least one measured outcome (patient satisfaction questionnaire) have not been adequately reported.	however clustering of measurements has been disregarded in the analyses.
16	Miresmaeili 2012	**Low risk** – "After selection of 20 patients, 10 were allocated to the test and the remaining 10 to the control group using the random numbers table."	**Unclear** – No mention throughout the paper.	**Unclear** - Blinding is impractical for both patients and clinician; outcome is objective, but was not assessed blindly.	**Unclear** – no mention of blinding throughout the paper; blinding should be possible.	**Low risk** – No drop-outs or patient losses are reported.	**High risk** – It is difficult to judge whether selective reporting is a problem, as no protocol exists; data not reported in adequate detail .	**Unclear** – intervention is administered by the clinician, so compliance is not a problem; however, clustering of measurements has been disregarded.
17	Seibold 2015	**Low risk** – patient assignment was randomized through the assignments of numbers from a random numbers list.	**Unclear** – sealed envelopes used; unclear if opaque.	**Unclear** - Blinding is impractical for both patients and clinician; however, outcome is objective and assessed blindly.	**Low risk** – blinding throughout the study until after the assesement of the data	**Low risk** – Two drop-outs were replaced during the first week. A total of 15% of the enrolled patients were lost ultimately, but this was assessed by comparison "per protocol" and "intention-to-treat" approaches.	**Unclear** – some amendments (mainly pertaining to the outcome measurement timepoints and primary outcome measure) are described, but it was judged that these should not introduce any bias .	**Unclear** – it is unclear if any trial violations existed, as the authors state that the sealed envelopes with the patient allocation were available in the study center for emergencies; emergencies are referenced in the text, but are neither listed nor explicitly excluded.
18	Senestraro 2013	**Unclear** – "For each participant, we used an electronic random number generator to select one affected tooth to serve as a control (no treatment), and we assigned the remaining teeth to the treatment group. Owing to reports of variable responses to reatment,27,28 allocation of teeth was biased toward the treatment group to maximize the	**Unclear** – No mention throughout the paper.	**Unclear** - Blinding is impractical for both patients and clinician; outcome is subjective, but was assessed blindly.	**Low risk** – Masking of all raters has been undertaken: the slides shown to the assessors were randomly sequenced. The lead investigator encoded image file names to mask the time point of the image. Another investigator outlined and measured WSL areas.	**Unclear** – a very high drop-out rate was seen (33%), while the study, although split-mouth seems not to be adequately balanced, as 46 and 20 teeth were allocated to the experimental and the control group; no further characteristics of the drop-outs are given.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – intervention is administered by the clinician, so compliance is not a problem; however, clustering of measurements has been disregarded.

		number of teeth treated": although allocation seems random, description is not adequate to ensure that no bias could have been introduced.						
19	Shell 2012	**High risk** – non-random allocation of patients: "The control and MI Paste Plus In Office treatment groups were filled first, one patient assigned to each group in an alternating manner until filled both groups were filled as evenly as possible. Then the same procedure happened with the groups using only at-home protocols"	**Unclear** – No mention throughout the paper	**Unclear** - Blinding is impractical for both patients and clinician; outcome is objective, but was not assessed blindly.	**High risk** – no mention of blinding throughout the paper, blinding could have been implemented	**Low risk** – no drop-outs or patient loss reported.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Unclear** – intervention is self-administered by the patient, but compliance with the instructions assessed in the study ("the same detailed oral and written instructions to each patient upon enrollment was an effort to standardized application across patient and treatment groups, as was the distribution and collection of at-home diary cards, which all patients returned."); however, clustering of measurements has been disregarded in the analyses.
20	Willmot 2004	**Low risk** – "Packs of mouthrinse and toothpaste were numbered and randomized by the dental products company according to a table of random numbers".	**Low risk** – "Packs were numbered 1 onwards by the pharmaceutical company and the test/control packs were randomized by that company according to a table of random numbers held by the company. The code was placed in a sealed envelope until the conclusion of both the trial and measurements": although opacity not stated, transparency measures adopted through central allocation were	**Low risk** – quadruple-blind: "Participants and researcher were unaware as to whether an intervention or control mouthrinse was being supplied.	**Low risk** – quadruple-blind: "The test and control interventions content were unknown to the researcher at imaging and measurement. " and "The curves for the study were calculated and produced before the andomization code was unlocked".	**Low risk** – 5 (19%) dropouts because of subsequently failing to attend for any further appointments; however, distribution of drop-outs in the groups is similar and it is unlikely that any differences in the two experimental groups would be responsible for dropouts.	**Unclear** – It is difficult to judge whether selective reporting is a problem, as no protocol exists.	**Low risk** – intervention is self-administered by the patient, but compliance with the instructions assessed in the study ("Participants were instructed to keep all empty bottles and tubes, and return them to the researcher at their next visit"); clustering of measurements in the analyses is not an issue; selection of assessed lesions per patients seems random and therefore was judged not to be prone to bias.

			judged adequate.					

Supplementary material 5. Details of the GRADE assessment for the main outcomes of this systematic review.

Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication bias	Large Effect	Dose Response	Residual Confounding
Outc 1: lesion area.	Starts from "high", due to the inclusion of randomized studies. There exists moderate risk of bias from methodological limitations of included trials; however, the sensitivity analysis excluding trials with high risk of bias did not find discordant results.	High heterogeneity, which affects both the decision for/against the intervention and the precision for this estimate; large part of the heterogeneity has been explained through subgroup analysis.	Directly relevant	Inadequate sample; the 95% CI includes both the null effect and small negative values, which indicates imprecision.	No assessment possible.	No reason to rate up	No dose response assessment.	Cannot be ruled out.
Outc 2: lesion fluorescence.	Starts from "high", due to the inclusion of randomized studies. There exists moderate risk of bias from methodological limitations of included trials; however, the sensitivity analysis excluding trials with high risk of bias did not find discordant results.	High heterogeneity, which affects both the decision for/against the intervention and the precision for this estimate; large part of the heterogeneity has been explained through subgroup analysis and measurement method.	Same as lesion area.	Inadequate sample; the 95% CI includes both the null effect and moderate to large negative values, which indicates imprecision.	Same as lesion area.	Same as lesion area.	Same as lesion area.	Same as lesion area.
Outc 3: lesion improvement/regression.	Starts from "high", due to the inclusion of randomized studies. No serious reason to downgrade (in 1/3 trials the personnel/patients were not blinded; but outcome assessment was blind).	Low heterogeneity; no reason to downgrade.	Same as lesion area.	Inadequate sample; the 95% CI includes both the null effect and moderate positive/negative values, which indicates imprecision.	Same as lesion area.	Same as lesion area.	Same as lesion area.	Same as lesion area.

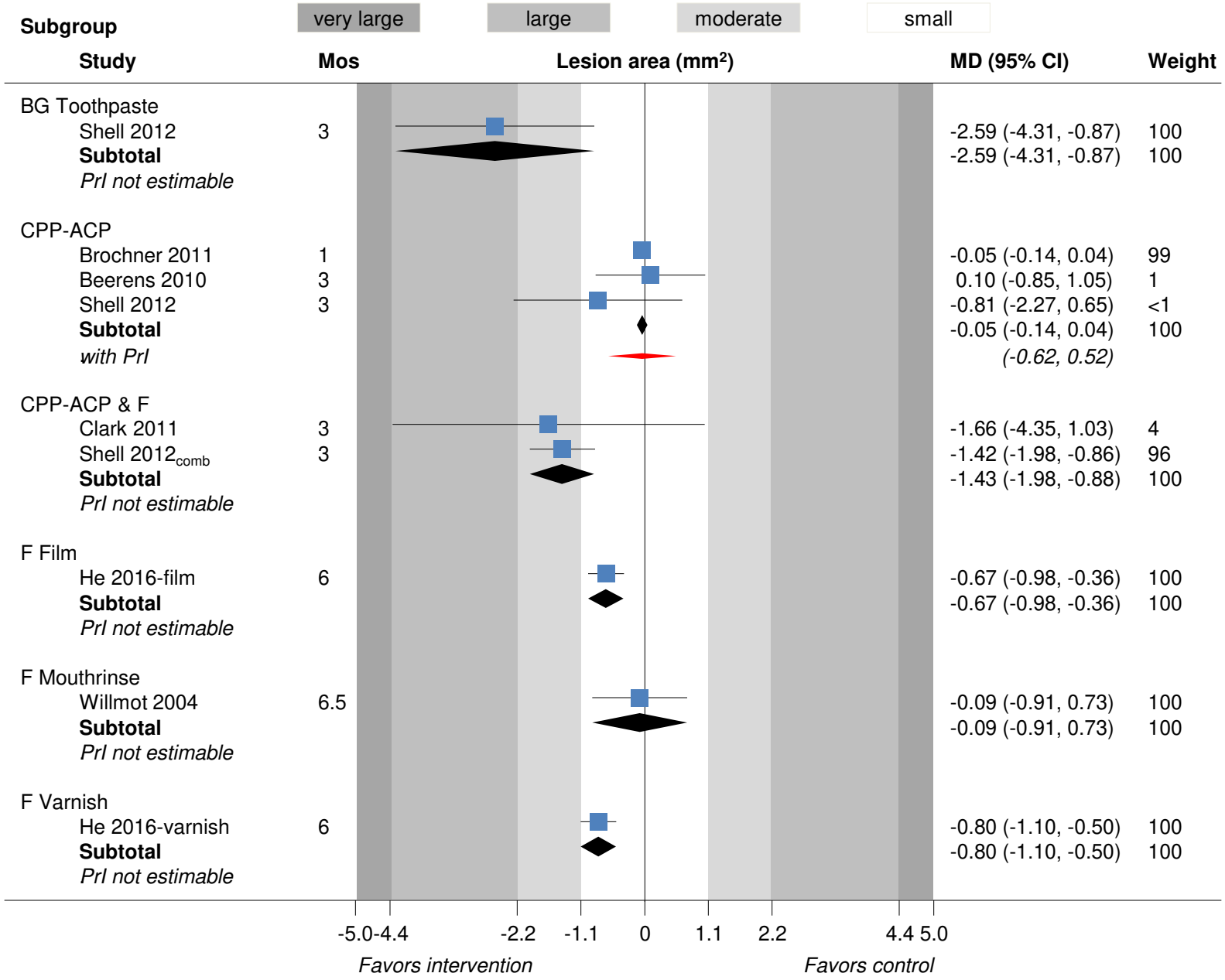
Outc, outcome; CI, confidence interval.

Supplementary material 6. Results of the subgroup analyses/meta-regressions for meta-analyses with at least three included trials.

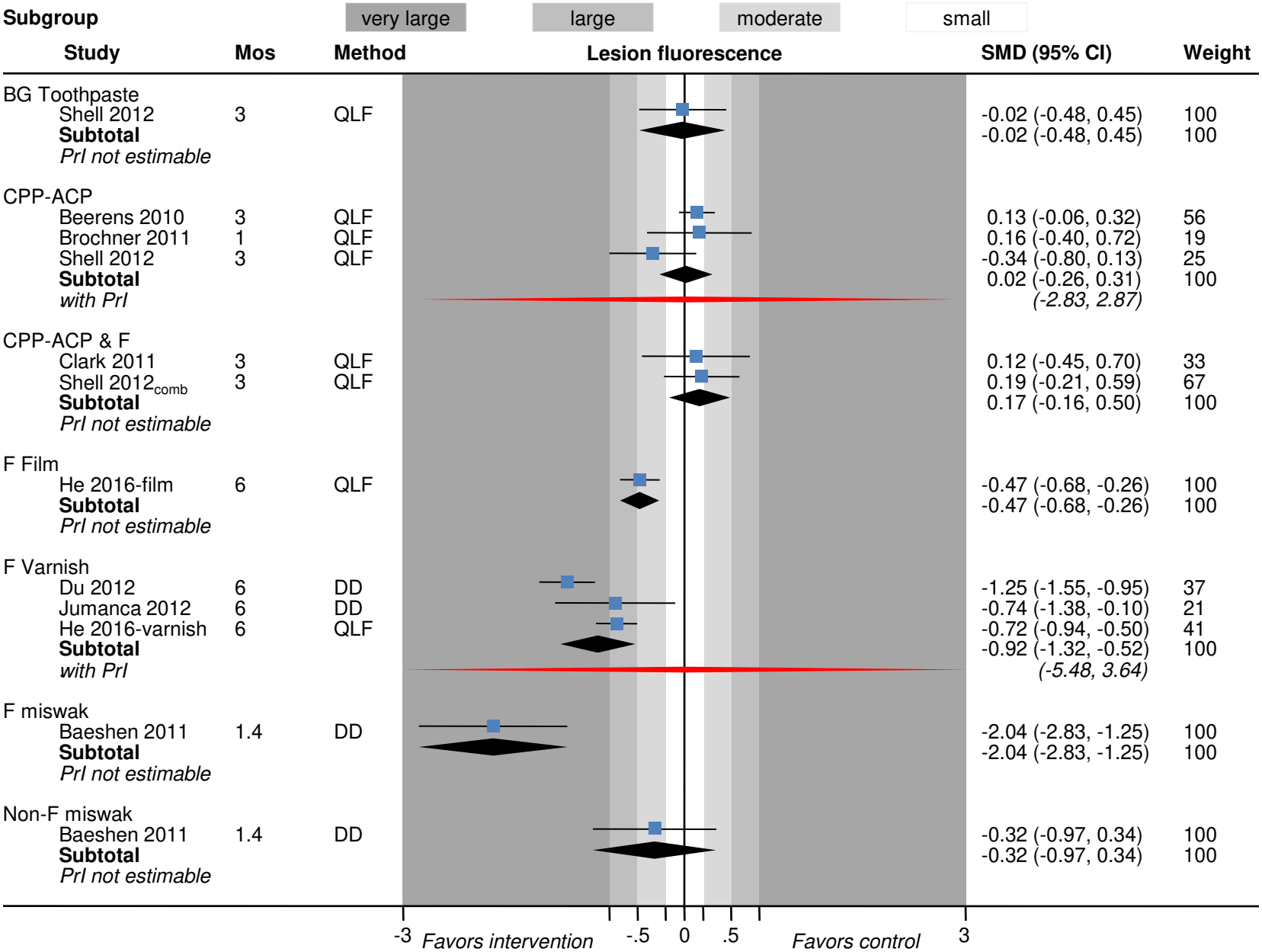
		WSL area					Fluoresence (QLF/DD)					Invisible /regressed WSLs			
		n	**MD**	**95% CI**	**P_{SG}**		**n**	**SMD**	**95% CI**	**P_{SG}**		**n**	**OR**	**95% CI**	**P_{SG}**
Intervention	BG toothpaste	1	-2.59	-4.31,-0.87	0.033		1	-0.02	-0.48,0.45	0.031		-	-	-	0.633
	CPP-ACP	3	-0.05	-0.14,0.04			3	0.02	-0.27,0.31			2	1.10	0.55,2.19	
	CPP-ACP with F	2	-1.43	-1.98,-0.88			2	0.17	-0.16,0.50			-	-	-	
	F film	1	-0.67	-0.98,-0.36			1	-0.47	-0.69,-0.26			-	-	-	
	F mouthrinse	1	-0.09	-0.91,0.73			-	-	-			-	-	-	
	F varnish	1	-0.80	-1.10,-0.50			3	-0.92	-1.32,-0.52			-	-	-	
	F gel	-	-	-			-	-	-			1	0.70	0.30,1.65	
	F miswak	-	-	-			1	-2.04	-2.83,-1.25			-	-	-	
	Non-F miswak	-	-	-			1	-0.32	-0.97,0.34			-	-	-	
Follow-up duration	Per month increase	6	-0.03	-0.43,0.37	0.843		8	-0.20	-0.37,-0.02	0.032		3	0.86	0.05,15.70	0.633

WSL, white spot lesion; QLF, Quantitative light-induced fluorescence; DD, DIAGNOdent; n, number of included studies; MD, mean difference; CI, confidence interval; P_{SG}; P value for differences from subgroup analysis/meta-regression; OR, odds ratio; BG, bioactive glass; CPP-ACP, casein phosphopeptides - amorphous calcium phosphate; F, fluoride.

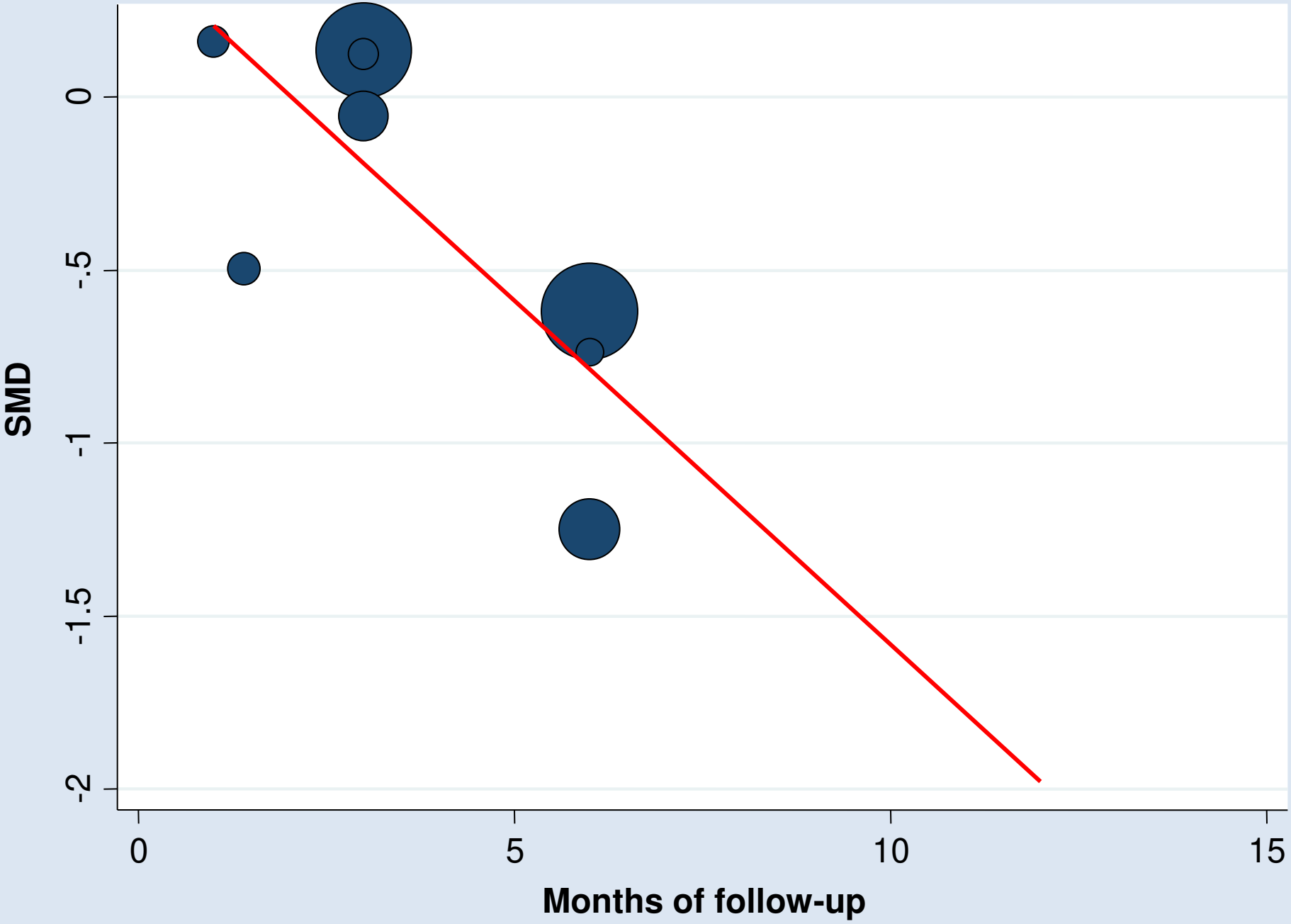
Supplementary material 7. Contour-enhanced forest plot of the treatment effects on white spot lesion area according to the intervention used. Color contours indicate increasing effect magnitude from the middle to the ends of the forest plot: small effects (white); moderate effects (light grey); large effects (dark grey); and very large effects (darker grey). Mos, months of follow-up; MD; mean difference; CI, confidence interval; $_{comb}$, combined trial arms; and PrI, predictive interval. Studies on the left and the right side of the middle line favor the intervention and the control group, respectively.



Supplementary material 8. Contour-enhanced forest plot of the treatment effects on white spot lesion fluorescence according to the intervention used. Color contours indicate increasing effect magnitude from the middle to the ends of the forest plot: small effects (white); moderate effects (light grey); large effects (dark grey); and very large effects (darker grey). Mos, months of follow-up; Method, method of outcome measurement; SMD; standardized mean difference; CI, confidence interval; $_{comb}$, combined trial arms; DD, DIAGNOdent; QLF, quantitative light-induced fluorescence; and PrI, predictive interval. Studies on the left and the right side of the middle line favor the intervention and the control group, respectively.



Supplementary material 9. Meta-regression for the association between change in lesion fluorescence [expressed as Standardized Mean Difference (SMD)] and the months of follow-up of each included trial.

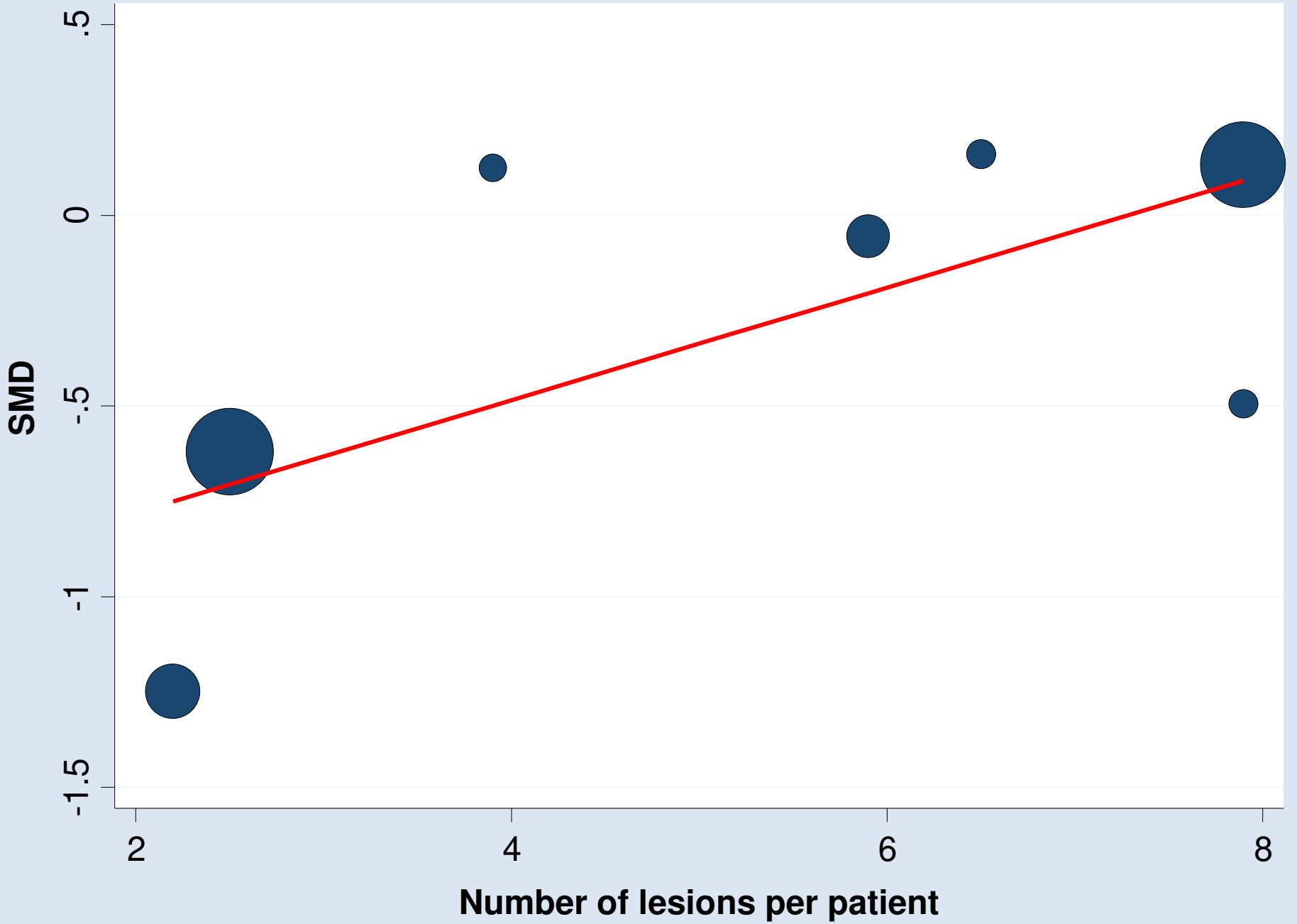


Supplementary material 10. Details of the performed sensitivity analyses.

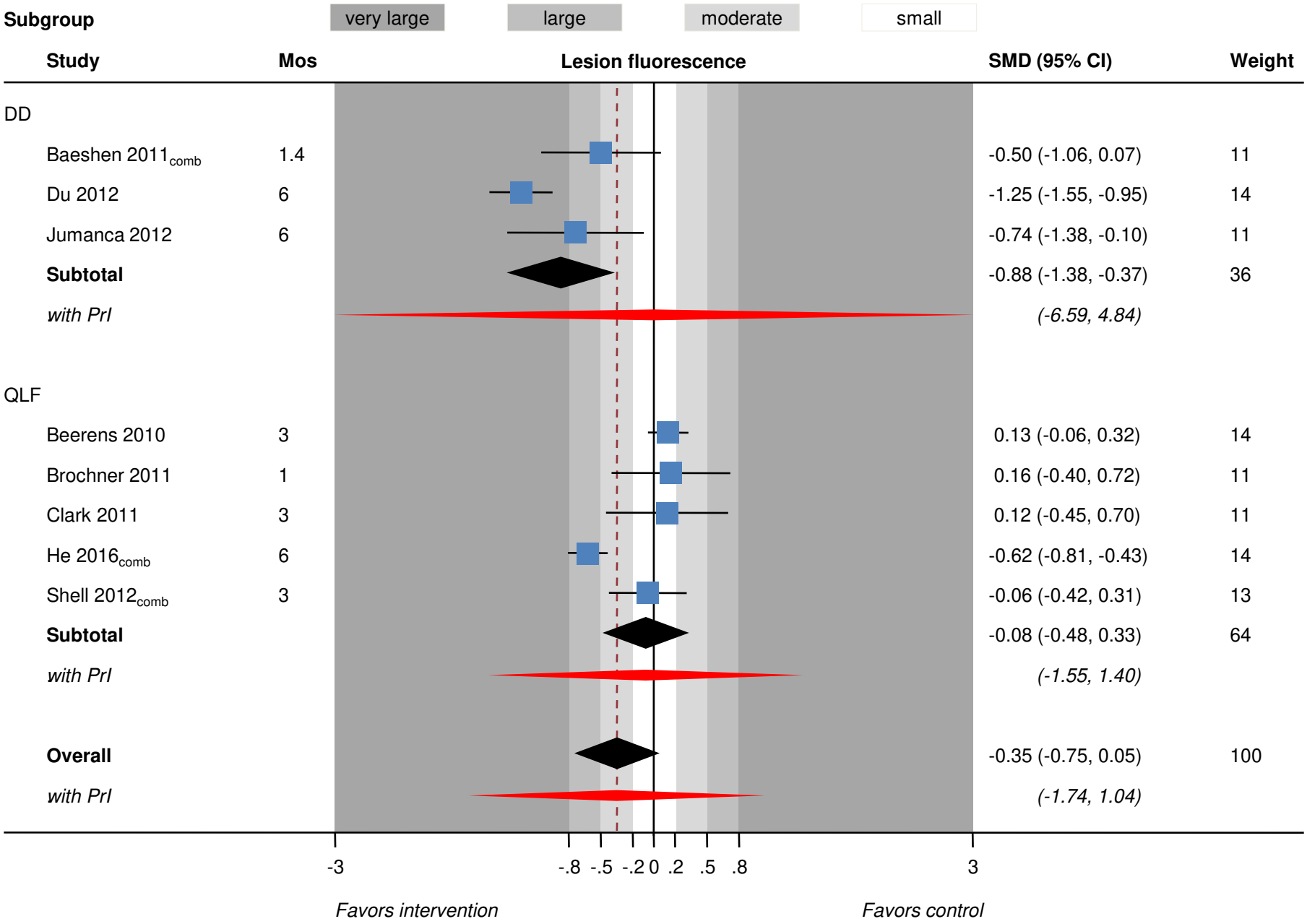
Category	Subgroup	Lesion area					Lesion fluorescence					Invisible/regressed lesions			
		n	MD	95% CI	P		n	SMD	95% CI	P		n	OR	95% CI	P
Measurement	Photograph (lesion area) / DIAGNOdent (lesion fluorescence)	1	-0.09	-0.91,0.73	0.568		3	-0.88	-1.38,-0.37	0.036		-	-	-	-
	QLF	5	-0.56	-1.12,-0.01			5	-0.08	-0.48,0.33			-	-	-	
Lesion/patient	Per additional lesion/ patient	5	0.15	-0.41,0.71	0.459		7	0.15	-0.04,0.33	0.097		-	-	-	-
Risk of bias	Low or unclear	3	-0.38	-0.95,0.18	0.521		3	-0.57	-1.30,0.16	0.363		2	1.12	0.48,2.59	0.722
	High	3	-0.86	-2.14,0.42			5	-0.17	-0.48,0.14			1	0.82	0.52,1.28	

N, number of studies; MD, mean difference; CI, confidence interval; SMD, standardized mean difference; OR, odds ratio; QLF, quantitative light-induced fluorescence.

Supplementary material 11. Meta-regression for the association between change in lesion fluorescence [expressed as Standardized Mean Difference (SMD)] and the number of assessed lesions per patient.



Supplementary material 12. Forest plot for the sensitivity analysis of the meta-analysis on lesion fluorescence according to the evaluation method used.



Supplementary material 13. GRADE summary of findings table for the sensitivity analyses of this systematic review according to the various interventions.

Outcomes	Intervention	Illustrative comparative effects (95% CI)		Trials	GRADE*	Significant effect
		Control	Intervention			
		Assumed change	Corresponding change			
Lesion area	BG toothpaste	Mean lesion shrinkage of 0.37 mm^2 in the control groups.	They shrink by 2.59 mm^2 more (95% CI: 0.87 to 4.31 mm^2 more).	1	⊕⊕⊕⊖[a,b]	Yes
	CPP-ACP		They shrink by 0.05 mm^2 more (95% CI: 0.14 mm2 more 0.04 mm2 less).	3	⊕⊕⊖⊖[a,c]	No
	CPP-ACP & F		They shrink by 1.43 mm^2 more (95% CI: 0.88 to 1.98 mm^2 more).	2	⊕⊕⊕⊖[a]	Yes
	F film		They shrink by 0.67 mm^2 more (95% CI: 0.36 to 0.98 mm^2 more).	1	⊕⊕⊕⊕	Yes
	F mouthrinse		They shrink by 0.09 mm^2 more (95% CI: 0.91 mm2 more 0.73 mm2 less).	1	⊕⊕⊕⊖[b]	No
	F varnish		They shrink by 0.80 mm^2 more (95% CI: 0.50 to 1.10 mm^2 more).	1	⊕⊕⊕⊕	Yes
		Assumed change	Corresponding change			
Lesion fluorescence	BG toothpaste	Mean enamel fluorescence increase by 1.07% in the control groups.	Fluorescence increases 0.05% more (1.20% more to 1.13% less)	1	⊕⊕⊖⊖[a,c]	No
	CPP-ACP		Fluorescence increases 0.02% less (0.26% more to 0.31% less)	3	⊕⊕⊖⊖[a,d]	No
	CPP-ACP & F		Fluorescence increases 0.17% less (0.16% more to 0.50% less)	2	⊕⊕⊖⊖[a,c]	No
	F film		Fluorescence increases 0.47% more (0.26% to 0.68% more)	2	⊕⊕⊕⊕	Yes
	F varnish		Fluorescence increases 0.92% more (0.52% to 1.32% more)	3	⊕⊕⊕⊕[e]	Yes
	F miswak		Fluorescence increases 2.04% more (1.25% to 2.83% more)	1	⊕⊕⊕⊖[a]	Yes
	Non-F miswak		Fluorescence increases 0.32% more (0.97% more to 0.34% less)	1	⊕⊕⊕⊖[a,d]	No
		Assumed risk per 1000 lesions	Corresponding risk per 1000 lesions			
Improvement/regression of the lesion	CPP-ACP	587 lesions per 1000 regress in the control groups.	59 lesions more regress (264 fewer to 699 more)	2	⊕⊕⊕⊖[d]	No
	F gel		176 lesions fewer regress (411 fewer to 382 more)	1	⊕⊕⊕⊖[d]	No

a-risk of bias from methodological issues; downgrade.
b-imprecision, which however doesn't affect the decision for/against the intervention; only the precision of the estimate; don't downgrade.
c-heterogeneity; downgrade.
d-imprecision, which affects both the decision for/against the intervention and the precision of the estimate; downgrade.
e-large effect magnitude in the absence of other serious issues; upgrade.

Supplementary material 14. List of persons contacted in this systematic review for clarifications or missing data.

AA	Trial entry	Inquiry	Contact	Status
1	[No authors included] {NCT00670618} A Prospective, Randomized Clinical Study on the Effects of Casein Phosphopeptide-amorphous Calcium Phosphate (CPP-ACP) Paste on Plaque, Gingivitis and White Spot Lesions in Orthodontic Patients - Part 2. Status: Recruiting.	Trial status	S. Dauwe / V. Noens (undelivered); G. De Pauw (10.7.16)	No response.
2	[No authors included] {NCT00670670} A Prospective, Randomized Clinical Study on the Effects of Casein Phosphopeptide-amorphous Calcium Phosphate (CPP-ACP) Paste on Plaque, Gingivitis and White Spot Lesions in Orthodontic Patients - Part 1. Status: Recruiting.	Trial status		
3	[No authors included] {NCT01344473} A Trial of Tooth Mousse to Remineralise Post-orthodontic Treatment White Spot Lesions. Status: Completed.	Trial status	D. Bearn (10.7.16)	No response.
4	[No authors included] {NCT01500187} Fluoride Varnish for Treatment of White Spot Lesions. Status: Completed.	Trial status	F. Garcia-Godoy (10.7.16)	Answered (11.7.16) and clarified; trial is not published.
5	Akin M, Basciftci FA. Can white-spot lesions be treated effectively? Angle Orthod 2012;82(5):770-775.	Study design	M. Akin (10.7.16)	No response.
6	Artun J, Thylstrup A. Clinical and scanning electron microscopic study of surface changes of incipient caries lesions after debonding. Scand J Dent Res 1986; 94: 193–201.	Study design	J. Artun (10.7.16)	Undelivered e-mail
7	Kleber CJ, Milleman JL, Davidson KR, Putt MS, Triol CW, Winston AE. Treatment of orthodontic white spot lesions with a remineralizing dentifrice applied by toothbrushing or mouth trays. J Clin Dent. 1999;10(1 spec no):44–49.	Study design	C.J. Kleber (10.7.16)	Answered (11.7.16) and clarified; trial is not randomized.
8	Zhou CH, Sun XH, Zhu XC. [Quantification of remineralized effect of casein phosphopeptiode-amorphous calcium phosphate on post-orthodontic white spot lesion]. Shanghai Kou Qiang Yi Xue. 2009 Oct;18(5):449-54.	Study design	X.C. Sun (10.7.16)	No response.
9	Agarwal A, Pandey H, Pandey L, Choudhary G. Effect of Fluoridated Toothpaste on White Spot Lesions in Postorthodontic Patients. Int J Clin Pediatr Dent 2013;6(2):85-88.	Clustering-free data or raw data	A. Agarwal (31.7.16)	No response.
10	Aljehani A, Yousif MA, Angmar-Mansson B, Shi XQ. Longitudinal quantification of incipient carious lesions in postorthodontic patients using a fluorescence method. Eur J Oral Sci 2006;114(5):430-4.	Clustering-free data or raw data	A. Aljehani (31.7.16)	No response.
11	Miresmaeili A, Darban H, Mahjub H, Yosefi F, Mollabashi V. Effect of Fluoride Varnish on Improvement of Surface Decalcifications after Fixed Orthodontic Treatment. Avicenna Journal of Dental Research. 4(2): 15-23.	Clustering-free data or raw data	A. Miresmaeili (31.7.16)	Answered (9.8.16); sent data.
12	Seibold LA. Das Einfluss von wöchentlichen 1,25%igen Fluorid- oder Placebogel-Anwendungen auf die Entwicklung von Initialkaries-Läsionen nach Multibracket-Behandlung. Doctoral Thesis, University of Giessen, 2015.	Clustering-free data or raw data	S. Ruf (31.7.16)	Answered (18.8.16); data could not be released on time without the sponsor's consent.
13	Senestraro SV, Crowe JJ, Wang M, Vo A, Huang G, Ferracane J, et al. Minimally invasive resin infiltration of arrested white-spot lesions: a randomized clinical trial. Journal of the American Dental Association (1939). 2013;144(9):997-1005. Epub 2013/08/31.	Clustering-free data or raw data	S. Senestraro (31.7.16)	Answered (5.8.16); asked the statistician to provide data.

Supplementary material 15. Additional information for this systematic review

Author contributions

TE and SNP conceived the idea. DH and SNP wrote the first draft of the protocol. DM, MHZ, SNP, and TE revised the protocol. SNP performed the literature searches and extracted search hits. DH did screening by title, abstract, fulltext, data extraction, and risk of bias, while MHZ checked all procedures afterwards in duplicate, and SNP resolved discrepancies. SNP handled communications with trialists and performed the statistical analysis. DM wrote the first draft of the manuscript. DM, MHZ, SNP, and TE assisted in the interpretation of the results and revised the manuscript draft. TE submitted the manuscript, is the guarantor and responsible for the accuracy of the data and for future updates of the review.

Post hoc changes to the protocol

- The outcomes chosen for the GRADE analyses were modified, according to the trials that were identified. We reduced the number of included outcomes from 7 that were planned in the protocol to 3, as these were the only ones with meta-analysis possible. All outcomes that were reported from the studies are listed in the paper.
- We used the standardized mean difference as effect measure in one instance, as the same outcome (enamel fluorescence) was measured with two devices (QLF imaging and DIAGNOdent) and the sensitivity analyses indicated that differences existed between the two measurements (one measurement method resulted in twice the SDs of the other methos—so the SMD was chosen to pool these).
- Several additional subgroup analyses were planned, but could not be performed.

- The number needed to treat was planned to be used to clinically translate the results of statistically significant meta-analyses of binary outcomes, but no significant binary outcomes existed.
- We considered *post hoc* to conduct a network meta-analysis to combine direct and indirect evidence and rank the available treatments according to their efficacy. Given however, the scarce comparisons between some treatments, the risk of bias problematic, and the fact that for the meta-analysis with the most studies (outcome of fluorescence) variation in the outcome measurement method was observed, we choce not to perform this *post hoc* analysis.

Supplementary material 16. Network plot showing the available comparisons for the meta-analysis with the largest number of contribution studies (enamel fluorescence) along with number of trials for each comparison and their risk of bias. The plot was considered *post hoc* to explore the feasibility of a network meta-analysis, which was however, not conducted.